RECENT ADVANCES IN ORGANIC CHEMISTRY

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RECENT ADVANCES IN ORGANIC CHEMISTRY

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WITH AN INTRODUCTION BY
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IN UNIVERSITY COLLEGE, LONDON

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To

MY FATHER AND MOTHER

PREFACE TO THE FOURTH EDITION

THE excerpts from previous prefaces printed below will enable the reader to see the main ideas which have been kept in view since the inception of this book in 1908. The demand for a fourth edition within little more than a year after the publication of the third edition seems to show that this method of treating the subject has been acceptable to the chemical public.

In writing a book such as this, several difficulties have to be avoided. In the first place, it is essential to ensure that the text does not degenerate into a mere series of arid abstracts of authors' papers, for nothing is duller than chemical pemmican.

Secondly, since it may reasonably be assumed that some readers are not perfectly acquainted with the earlier history of every field of research described in the volume, it is necessary to provide a foundation upon which the description of recent work can be based. For example, to restrict an account of the work done upon the terpenes to papers published only within the last three years would be to distort the whole perspective of the subject and render the book unreadable. The title, "Recent Advances," was purposely chosen so as to permit the inclusion of earlier work wherever this was necessary; and the words must not be interpreted as meaning that *only* the very latest papers in any branch will be described.

In the third place, the limitations of space complicate the author's problem. Out of the many fields of interest which the subject contains, he has to make a selection, since otherwise the book would be too unwieldy. How is the process of selection to be carried out? In the present volume an attempt has been made to hold the balance evenly between the theory and the practice of the subject, so as to give as fair a representation of the whole field as possible. Further, the general continuity of Organic Chemistry has influenced the selection to some extent, so that information given in one chapter may be collated with facts described in other parts of the book.

Finally, at this time of day there is very little excuse for writing an advanced work which is a mere reproduction of facts and theories thrown together without critical spirit. The advancement of knowledge is promoted mainly by the study of those facts which cannot be accounted for by current theories; and it is essential to avoid the impression that our present views are the only hypotheses capable of fitting our ever-extending acquaintance with phenomena. Organic Chemistry is a subject of the greatest interest; and it seems to be a duty of those who expound it to bring out strongly some points which will appeal to younger investigators and stimulate them to go further into the many questions which are still without an answer.

In the present edition, a new chapter has been written with the object of calling attention to some of the problems which still lie open to solution among the commonest facts of the text-books; and it is hoped that this may be of interest to the younger generation of investigators, and may direct their attention to kindred questions among the simpler organic compounds. The older chemists—among whom I now regretfully include myself—are often hampered by long-continued reliance upon the current conceptions when they attempt to face new problems; and it is to the rising generation that we must look for the results which will follow from the impact of fresh minds upon the knowledge which has been acquired. Complexity and profundity are not necessarily cognate terms; and a vast field of research still awaits us among the simplest organic compounds.

The chapter on the polypeptides has been extended by a section which traces the connection between the synthetic materials on the one hand, and the naturally occurring proteins and their derivatives on the other; but no attempt has been made to do more than give an outline sketch of protein chemistry. Those who wish full details on matters such as this will seek their information in volumes specially devoted to the subject; for attempts to deal in any detail with such a complex branch of chemistry within the scope of a chapter appear to end in dullness and, what is worse, to give a wrong idea of the state of our knowledge.

In other parts of the book the principal advances of the last year have been dealt with in appropriate sections.

In conclusion, I wish to express my indebtedness to Professor Collie, F.R.S., and Professor Smiles, F.R.S., O.B.E., for assistance in the preparation of the present edition. My thanks are again due to my reviewers for their kindly encouragement, and also for help in indicating how the book could be improved.

ALFRED W. STEWART.

THE SIR DONALD CURRIE LABORATORIES,
THE QUEEN'S UNIVERSITY, BELFAST,
August, 1920

EXTRACTS FROM THE PREFACE TO THE FIRST EDITION

In dealing with Organic Chemistry two courses are open; for we may consider the matter either historically or from the synthetic point of view. In the present volume the second method has been adhered to as far as possible; and when the synthesis of a substance is known, its constitution has been deduced from the method of formation rather than from its decomposition products. The latter, when important, are reserved for consideration after the constitution has been demonstrated. For the sake of clearness, each step in the syntheses has been treated in a separate section, so that at any moment the reader can see exactly how far he has advanced, and can easily refer back to any stage which he may wish to read again.

University College, London,
September, 1908.

EXTRACT FROM THE PREFACE TO THE SECOND EDITION

When writing the first edition, I tried to bear in mind that science is not a mere collection of data, but is rather a rapidly changing series of hypotheses by means of which we attempt to group the facts with which we are acquainted: and consequently I endeavoured (as one of my reviewers put it, more clearly than I could do) "to illustrate the principles upon which modern chemistry moves—not stands—and to undermine the conservatism which exists in all but strikingly original minds." The reception accorded to the volume showed that this mode of regarding the subject is more general than I had anticipated.

The Sir Donald Currie Laboratories,
The Queen's University of Belfast,
October, 1910.

EXTRACT FROM THE PREFACE TO THE THIRD EDITION

To keep the book in touch with the modern trend towards the chemistry of natural products and substances of physiological interest, a new chapter has been written containing certain theories bearing upon the synthesis of compounds in vegetable and animal organisms.

One error, common to nearly all text-books, has, it is hoped, been avoided in this one. On comparing the average text-book's statements with those in the original papers, one is frequently struck by the manner in which a tentative suggestion in the journal takes on a dogmatic tone when transferred to the text-book; and in this way a wholly erroneous view of the actual facts is put afloat among those who seldom consult the original literature. Such mishaps cannot altogether be avoided, but it is believed that in the present volume a successful effort has been made to approach the spirit of the originals, and I have striven not to force any point beyond its legitimate range.

An attempt has been made to write in a critical spirit, as was done in the two previous issues. It is possible that readers may detect a certain bias against the flood of synthetic material which pours chiefly from the German laboratories. Lest this should be attributed to a reconsideration of the value of German science in the light of the war, it may be mentioned that exactly the same views were expressed in earlier editions; I have seen no reason to modify my opinions on the subject.

The Physical Chemistry Department,
The University of Glasgow,
September, 1918.

INTRODUCTION

At the present time it is not altogether easy to say on what lines a text-book of Organic Chemistry should be written. To state in the preface that the Author "hopes it will supply a long-felt want" is not always an injudicious method of announcing the Author's belief in the readers of text-books. For if the "long-felt want" of the public is to have a re-statement of all the old facts once more, with nothing new, no critical faculty shown, and an obvious lack of evidence that the book can be used to broaden our outlook on other sciences as well as chemistry, then no doubt the desire of the public for the time being is satisfied.

It is certainly to be regretted, however, that so many books on Organic Chemistry are published regardless of the fact that Organic Chemistry is a growing science. If one wants to know about a new piece of country, to obtain a large number of photographs all taken from the same place, is obviously a foolish thing to do. Yet book after book on Organic Chemistry is published, covering the same ground, with a fine disregard of the fact that to the pioneers the outlook is constantly changing. A book that has practically nothing new in it, except the description of a few more compounds, is unnecessary. Fortunately, however, there are some text-books which are not mere narrations of facts, and which do point out not only what has been done, but what might be accomplished, and which do make the reader think.

At no time, moreover, is a change wanted in the method of writing text-books more than at present. Deluged as we are with unnumbered *facts* which have *often neither* explanation nor obvious connection with one another, Organic Chemistry has become a vast rubbish heap of puzzling and bewildering compounds. The sanguine chemist expresses a hope that some day, perhaps, a few of these may be useful. All knowledge ought to be useful, even that obtained by the manufacture of the thousands of new substances which are annually produced in chemical laboratories. But where is it to stop? When one looks at Beilstein's "Handbook" or Richter's "Lexicon," or takes up a current volume of any chemical journal, how many of the compounds or the papers are of interest even to the most enthusiastic chemist? The game of permutations and combinations goes on, the chief object apparently being merely to supplement the already existing myriads of laboratory-made organic compounds.

How, out of all this undigested mass, is the writer of a text-book to glean what is of interest or tell what ought to be taken and what left? The result is that many text-books are not much more than abridged chemical dictionaries. The only tax on the reader's mind is to remember as many facts as possible. The text-book is rare that stimulates its reader to ask, Why is this so? or, How does this connect with what has been read elsewhere?

Indeed, it is not inconceivable that a useful text-book might be written on the constitutional formula of a single organic compound; for instance, alcohol. Its manufacture and physical properties would have to be considered. This would necessitate a knowledge of many typical organic compounds, and also of many kinds of reactions. The evidence thus obtained could then be summed up for the purpose of expressing all these facts by the chemical formula. Here the theory of the constitution of organic compounds would have to be dealt with, beginning with the ideas in vogue at the beginning of last century: Berzelius' Electro-chemical Hypothesis, of how the nature of the elements present had the chief influence on the properties of the compound; Dumas' Type-theory, and how he was the first (about 1840) definitely to recognize the arrangement of the atoms in the molecule: how this idea took about a quarter of a century to get into the text-books; how Frankland, in 1852, started the idea of valency, from which sprang the modern ideas of chemical structure and linking of atoms; how Kekulé first definitely put forward the idea of the quadrivalence of carbon; how Crum Brown, in 1865, suggested the present form of graphic formulæ and pointed out that they were "not to indicate the physical but merely the chemical position of the atoms." All these ideas have more or less centred round alcohol and its derivatives; and any one who carefully had followed the reasoning that led to these various mechanical methods for representing by a chemical formula the molecular structure of organic compounds would be in a position easily to recognize that our present ideas must in future suffer change just as they have done in the past.

Berzelius' ideas were those of a great mind; but in his day narrower theories were necessary for the more detailed development of chemistry. Dumas' Type-theory, on the other hand, was too narrow; it was a very restricted system of classification, and one that led to many false analogies. Up to the present day, the Frankland-Kekulé conceptions of valency and graphic formulæ have held their own, but there are signs that these, too, will have to be modified; physical as well as chemical properties will have to be accounted for.

The present volume should be of great use to students of organic chemistry. The subject-matter is put in an eminently lucid form that enables the reader easily to follow all the arguments, while at the same time his critical faculty is stimulated. The book, moreover, is unlike so many modern text-books in that it is not a mere compilation of facts; several novel theories on organic chemistry are dealt with, theories that up to the present can hardly be said to have assumed definite shape, but which rather point to the paths along which the pioneers of the science are likely to go in the immediate future.

J. NORMAN COLLIE.

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CHAPTER I

ORGANIC CHEMISTRY IN THE TWENTIETH CENTURY

In the form in which it exists to-day, organic chemistry may be said to take its root in the work of Frankland[1] at the middle of last century. Once the doctrine of the constancy of valency was accepted, the way was open for Couper[2] and Kekulé[3] to bring order into the vast mass of material which had been accumulated in earlier times; while, later, van't Hoff[4] and Le Bel[5] carried the ideas of molecular arrangement out of two dimensions into three and laid the foundation of our present views. Following in the track of these pioneers, the chemists of the latter half of the nineteenth century rapidly developed the theoretical side of the subject; while, on the other hand, the modern structural formulæ lent to synthetical work a certainty which had previously been unknown.

Despite the Briarean efforts of the synthetic school, it is safe to say that the latter half of the nineteenth century will be regarded as a time when theoretical speculation played the main part in the development of the subject. Of the hundred thousand organic compounds prepared during that time, the majority were still-born and their epitaphs are inscribed in Beilstein's Handbook. Compared with the great clarifying process which laid the basis of our modern views, they weigh but little in the balance.

The new century opened under different auspices. At first it seemed as though the discoveries in electronic physics would have their reaction upon our structural views; but though several attempts[1] have been made in this region of the subject, organic chemists in general have not welcomed them with anything like whole-hearted encouragement. There is a feeling, apparently, that in abandoning the usual structural formulæ and replacing them by electronic symbols the subject is being complicated instead of simplified; and this feeling, whether it be due to scientific caution or to mere conservatism, has certainly carried the day for the present. It seems probable that the lack of a concrete model has been one of the drawbacks from which the new movement suffered. Structural chemistry and the conception of molecular asymmetry owed more than we can estimate to the fact that they could be illustrated by mechanical devices which rendered them easy of apprehension by the multitude; and it seems possible that, if electronic models could be contrived,[2] their appearance would stimulate the chemical imagination much more rapidly than any mere written efforts can do.

---

[1] Frankland, *Phil. Trans.*, 1852, 142, 417.

[2] Couper, *Phil. Mag.*, 1858, iv., 16, 104.

[3] Kekulé, *Annalen*, 1866, 137, 129.

[4] van't Hoff, *Voorstell tot uitbreiding der structuur formules in de ruimte* (1874).

[5] Le Bel, *Bull. soc. chim.*, 1874, ii., 22, 377.

During the last fifty years the flood of synthetic material, principally from the German laboratories, has tended to obscure the genesis of what we still, out of respect for tradition, term organic chemistry. In its early days the science was devoted to the study of compounds produced by natural methods in plants and animals; and it is interesting to find that during the new century a return has been made to the older field.

The twentieth century was hardly begun, when in 1903 Komppa devised a synthesis of camphor, and thus cleared up a problem which had engaged the attention of many investigators. Later came the work of Perkin and his school in the terpene group, which gave a fresh impetus to study in this branch of the subject.

---

[1] Nelson and Falk, *School of Mines Quarterly*, 1909, 30, 179; *J. Amer. Chem. Soc.*, 1915, 37, 274; Nelson, Beans, and Falk, *ibid.*, 1913, 35, 1810; Falk and Nelson, *ibid.*, 1910, 32, 1637; 1911, 33, 1140; *Falk*, *ibid.*, 1912, 34, 1041; Noyes, *ibid.*, 1912, 34, 663; Fry, *ibid.*, 1912, 34, 664; 1914, 36, 248, 262, 1085; 1915, 37, 885; 1916, 38, 1323, 1327, 1338; *Zeitsch. physikal. Chem.*, 1911, 76, 385, 398, 591; 1912, 80, 29; 1913, 82, 665; 1915, 90, 458; Stark, *Jahrb. Radioaktiv Electronik*, 1908, 5, 124; 1909, 6, 12; 1912, 9, 15; *Physikal. Zeitsch.*, 1912, 13, 585.

[2] Ramsay (*Proc. Roy. Soc.*, 1916, (A), 92, 451) devised a simple electrical model which may be capable of elaboration.

In the alkaloid series great strides have been made, both in determining constitutions and in devising synthetic methods of preparing the natural substances; whilst the examination of plants and the extraction from them of new alkaloids is proceeding apace.

In the carbohydrate group the problem which looms behind most of the modern investigations is the constitution of the celluloses; and the work carried out by Cross, Bevan, Purdie, Irvine and others is leading us gradually towards a solution of that intricate enigma. The celluloses have extremely complicated structures; and it is only by breaking up their molecules into simpler compounds and then identifying these that we can hope to determine the constitution of the parent substance. The first step in this direction is evidently to obtain and identify readily purifiable carbohydrate derivatives such as methyl ethers, acetyl derivatives, etc. Then by methylating or acetylating celluloses themselves previous to breaking them up, it may be possible to recognize among the decomposition products certain well-defined fragments which will permit of guesses being made at the structure of the original molecule.

Much more complicated is the riddle of the protein molecules. Although there is a surface similarity between proteins and celluloses owing to the fact that both molecular types are liable to fission under the action of hydrolysing agents, the decomposition products of the proteins are far more complex than those resulting from the break-down of celluloses. Fischer's work on the polypeptides has been a first step towards a more exact knowledge of the protein constitutions; but it is a very short step on a very long road.

The methods devised by Fischer in his investigation of the polypeptides served him later in his researches on the tannins. In 1912, he put forward the view[1] that the natural tannins were fully esterified glucoses in which digalloyl nuclei replaced the hydrogen atoms of hydroxyl groups; and this conception of the tannin structure was justified by his synthesis of penta-*m*-digalloyl-β-glucose, which closely resembles Chinese tannin in its properties. The structure of this compound may be represented by

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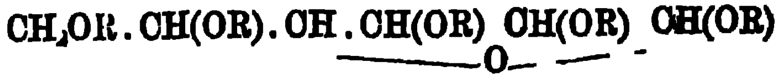
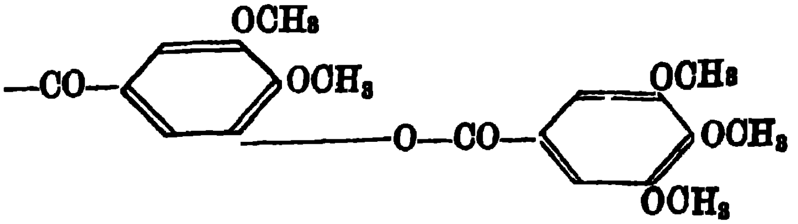
[1] For a full account see Fischer's lecture, *Ber.*, 1913, 46, 3253; also Fischer and Bergmann, *ibid.*, 1918, 51, 1760; 1919, 52 [B], 829.



$$CH_2OR.CH(OR).CH.CH(OR).CH(OR).CH(OR)$$

in which the radicle R is the digalloyl nucleus:—



Compounds of this type belong to what is termed the depside group, depsides being compounds obtained by linking the carboxyl radicle of a phenolic carboxylic acid to the hydroxyl radicle of a second molecule of the same compound. When two molecules are thus joined the compound is a didepside, when three molecules are linked together in the chain the product is termed a tridepside, and so on. For example, the formula

$$HO.C_6H_4.CO\ O\ C_6H_4\ CO\ O\ C_6H_4\ COOH$$

is that of a tridepside.

It must not be assumed, however, that Fischer's researches have given us the key to the structure of all classes of tannins, since hemlock tannin, for example, contains no sugar group in its structure and hence cannot be constituted in this way at all.[1]

Turning to natural pigments, it will be found that the present century has seen a great advance in our knowledge. Kostanecki's researches on the flavone derivatives established the constitutions of many of the natural dyes. Willstatter's work on chlorophyll has given us some insight into the nature of that mysterious substance, though it would be going too far to claim that even yet we know much about the chlorophyll structure; whilst in the field of flower pigments the same investigator has established the general character of the anthocyanins and has practically reduced future work to a stereotyped line.

The examination of the colouring matters of the blood and of the bile has opened up yet another branch of pure "organic chemistry"; and the parallelism established between hæmin and chlorophyll suggests most interesting reflections as to the origin of these two natural substances which play so great a part in animal and vegetable economy.

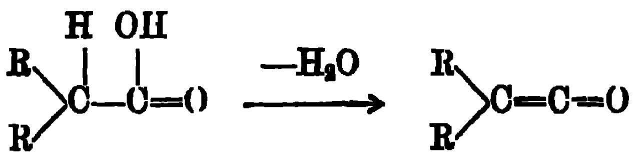
---

[1] Manning and Nierenstein, *Trans.*, 1919, 115, 662.

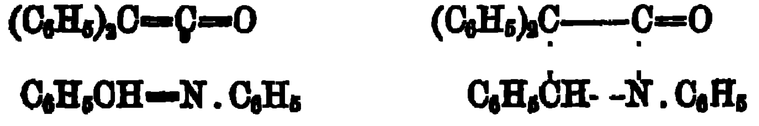
The Anglo-French synthesis of artificial rubber furnishes one of the most striking modern examples of international collaboration, and forms a happy augury for the future.

So much for the effects of a return to the original aims of organic chemistry. When the purely synthetic side of the subject is examined in turn, it must be admitted that the results are of less general interest. Of "new" compounds there is no lack; but of "interesting" substances there is a distinct dearth. Two classes, however, stand out with refreshing clearness from the chaotic mass of laboratory by-products: the ketens and the triphenylmethyl derivatives.

The ketens may be regarded as a new type of anhydride derived from acetic acid or its substitution products:—



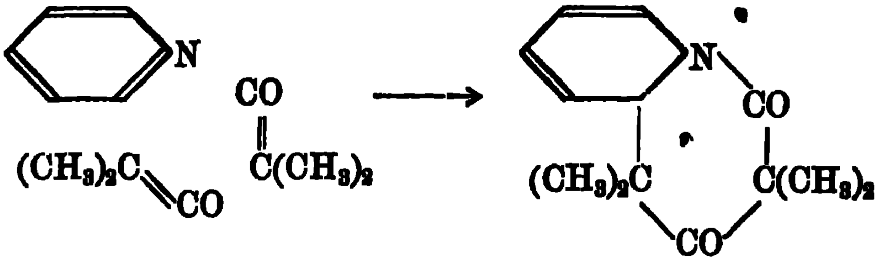
In virtue of the ethyleno-carbonyl grouping which they contain, the ketens are intensely active and unite with many reagents with the utmost readiness. Thus with water they regenerate the parent acids; with alcohol they yield the corresponding esters; with hydrochloric acid they give the chloro-derivatives of the parent acids; chlorine acts on them to produce chlor-acylchlorides, ammonia yields amides; aniline produces anilides; and on reduction they give aldehydes. Left to themselves, they polymerize with more or less rapidity to tetramethylene derivatives and more complex substances; and they readily oxidize in air. With compounds containing double linkages they combine with more or less readiness, forming cyclic compounds with four members in the ring:—



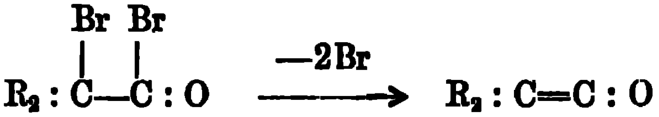
$(C_6H_5)_2C{=}C{=}O$ $\quad$ $(C_6H_5)_2C$——$C{=}O$

$C_6H_5CH{=}N.C_6H_5$ $\quad$ C_6H_5CH- -$N.C_6H_5$

In the case of certain cyclic bases a similar reaction results in the formation of what have been termed keten bases. Thus with pyridine and dimethyl-keten the product is dimethyl-keten-pyridine:



The keten class was discovered in 1905 by Staudinger,[1] and the method of preparation devised by him depends upon the removal of two atoms of a halogen from the halide of a halogen substituted acid by means of metals:—



$$R_2:\overset{Br}{\overset{|}{C}}-\overset{Br}{\overset{|}{C}}:O \xrightarrow{-2Br} R_2:C{=}C:O$$

Later, Wilsmore and Stewart[2] showed that the parent substance, keten itself, which had not then been isolated, could be obtained by treating acetic acid or acetone with an electrically heated wire, which removed water in the one case and methane in the second instance.

Though the ketens afford many points of interest, their actual bearing upon theory is not great. The triphenylmethyl and diphenylhydrazyl derivatives, on the other hand, suggest problems which go down to the very root of our ideas of valency. It is perhaps too soon to say that the study of this series will entirely modify our views on chemical affinity; but the progress which has been made certainly suggests that the last has not yet been heard of the question.

On the technical side organic chemists have not been idle. The great dye industry pours out its flood of colour; and although as a general rule its products have a commercial rather than a scientific interest, two classes deserve notice here.

Vat dyes are those which, like indigo, are almost insoluble in water, but yield on reduction leuco-compounds soluble in alkali. The actual dyeing process is carried out by impregnating the fabric with the leuco-compound and then allowing or forcing oxidation to take place. The earliest example of the anthraquinone vat dyes, indanthrene, was produced in 1901. It is prepared by fusing 2-amino-anthraquinone with alkali, or by condensing 1-amino-anthraquinone with itself:—

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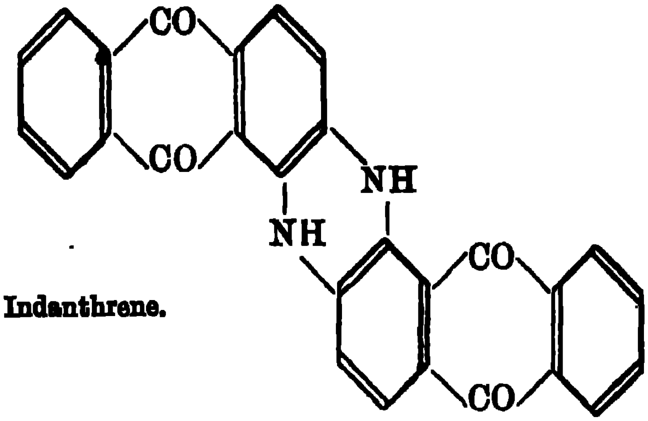
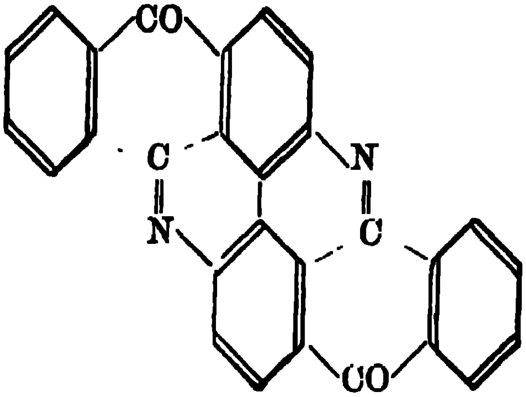
[1] Staudinger, *Ber.*, 1905, 38, 1735.

[2] Wilsmore and Stewart, *Nature*, 1907, 75, 510; Wilsmore, *Trans.*, 1907, 91, 1938.



Indanthrene.

To the same class belongs flavanthrene:—



Flavanthrene.

which can be produced by heating 2-amino-anthraquinone with alkali to a temperature higher than that required to form indanthrene. Indanthrene is a valuable dye-stuff of greater stability than indigo; whilst flavanthrene, though giving a blue vat, dyes cotton yellow.

Another class of anthraquinone vat dyes are the acyl derivatives of amino-anthraquinones. For the most part these are yellow or orange in colour, whilst the anthraquinone-imines vary in tint from orange to red or claret colour according to their constitution.

In 1906 Friedländer[1] discovered the thio-analogue of indigo in which the two imino groups are replaced by sulphur atoms; and this substance has become the foundation of a very extensive group of dyes. The following scheme shows one method of synthesis —

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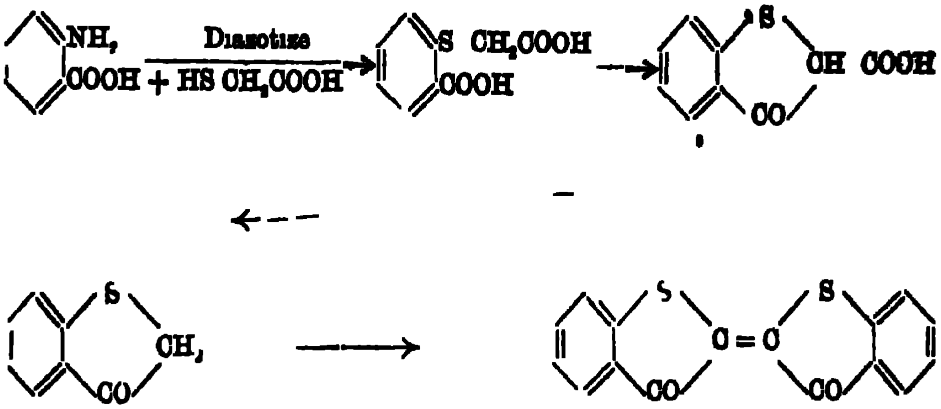
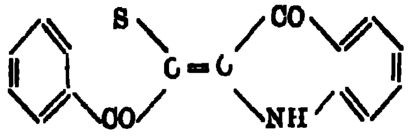
[1] Friedländer, *Ber.*, 1906, 39, 1060.



Thio indoxyl

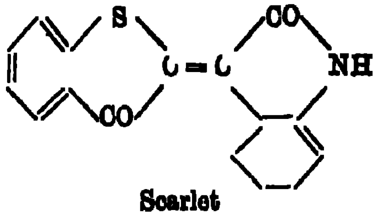
Thio indigo.

Thio-indigo imparts a reddish-violet colour to the fabric, and modified tints can be produced by using the amino or halogen derivatives Further changes in colour are obtained by condensing together one isatin and one thio-indoxyl group, producing mixed structures —



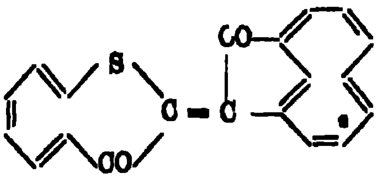
Violet A.

and



Scarlet

whilst by uniting thio-indoxyl with diketo-acenaphthenequinone the valuable dye thio-indigo scarlet is obtained —



Synthetic drugs have been produced in large numbers in recent years Of these the most important is salvarsan or 606, which is dihydroxy-diamino-arsenobenzene dihydrochloride. It has been used with success to kill the spirochaete which produces syphilis, though, of course, it has no effect in repairing the ravages already caused by the disease if treatment has been delayed. Another organic arsenic derivative employed is atoxyl (also known as arsamin or soamin), which is the mono-sodium salt of *p*-aminophenyl-arsenic acid. It is chiefly utilized in cases of sleeping sickness. Both of these drugs, if used incautiously, may produce blindness.

Numerous new local anæsthetics are now known, such as stovaine, novocaine, and β-eucaine, adrenaline has been synthesized; and the constituents of ergot are now manufactured for pharmacological purposes.

The modern explosive industry need not be described here. None the less, it has risen to heights which were not anticipated by any one before the war.

The new century has already seen the employment of fresh types of reagents; and some account of these must now be given. The most widely applicable of all is that which we owe to Grignard.[1] The rush to apply this new synthetic weapon exceeded anything previously known in the history of organic chemistry; indeed, the original discoverer was left almost out of the race; and hundreds of papers testified to the general eagerness to try the applicability of the magnesium alkyl derivatives to all sorts of problems. Owing to its simplicity and certainty the Grignard reaction stands almost in a class by itself.

Next to it comes the reduction method of Sabatier and Senderens,[2] in which a mixture of hydrogen and the substance to be reduced is passed over a heated layer of finely divided metal. This reaction also has been minutely studied; and the relative catalytic values of various metals have been tested.

A reagent which found wide application in the earlier years of the century is "Caro's acid," prepared by mixing potassium persulphate with concentrated sulphuric acid. The permonosulphuric acid thus formed is one of the most interesting oxidizing agents at our disposal. In general, it is powerful in action; but it may easily be regulated so that the most sensitive intermediate compounds can be isolated, as in the case of the production of nitroso-benzene from aniline.

Ozone is not exactly a new reagent in organic chemistry; but its real usefulness was not recognized until Harries made a thorough examination of its action. It attacks ethylenic linkages and forms ozonides which can be decomposed by water, yielding decomposition products of the original unsaturated compound. The reaction in the case of citral will be sufficient to show the results which are to be expected :—

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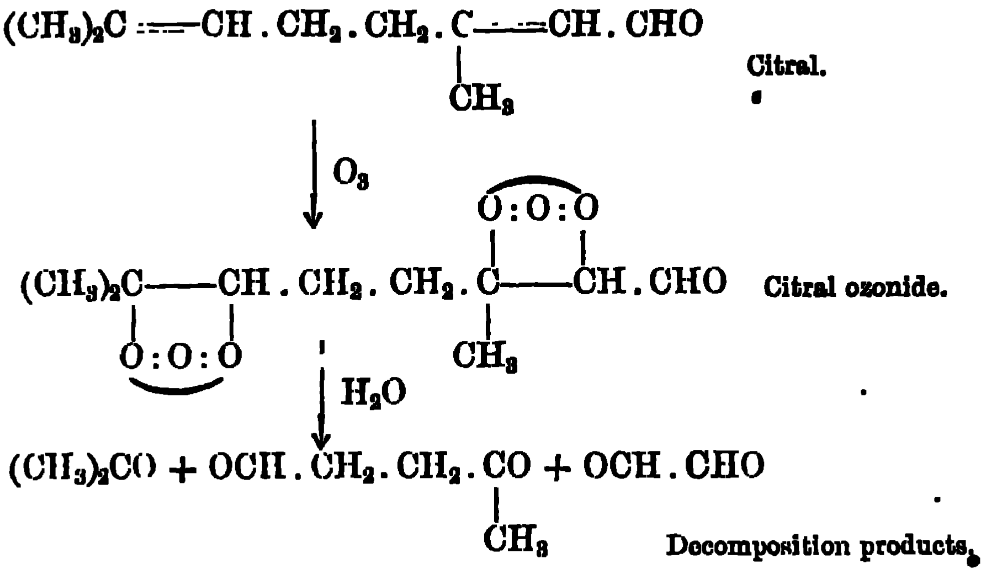
[1] Grignard, *Compt. rend.*, 1900, 130, 1322.

[2] Sabatier and Senderens, *Compt. rend.*, 1897, 124, 616.



$$(CH_3)_2C{=}CH.CH_2.CH_2.\underset{\underset{\displaystyle CH_3}{|}}{C}{=}CH.CHO \quad \text{Citral.}$$

$$\Big\downarrow O_3$$

$$(CH_3)_2\underset{\underbrace{O:O:O}}{C{-}CH}.CH_2.CH_2.\overset{\overbrace{O:O:O}}{\underset{\underset{\displaystyle CH_3}{|}}{C}{-}CH}.CHO \quad \text{Citral ozonide.}$$

$$\Big\downarrow H_2O$$

$$(CH_3)_2CO + OCH.CH_2.CH_2.\underset{\underset{\displaystyle CH_3}{|}}{CO} + OCH.CHO \quad \text{Decomposition products.}$$

It will be seen that the ozonide method furnishes a means of determining the constitution of ethylenic derivatives; but it must be noted that its application is limited by certain sharply defined conditions. The ease with which ozone acts upon the particular compound under test, the readiness with which the formed ozonide decomposes,* and the stability of other radicles in the nucleus against attacks by ozone all tend to circumscribe the utility of the reagent.

On the theoretical side of organic chemistry, to which we must now turn, Thiele's views have exerted a considerable influence during the century. It is very seldom that any theory is accepted immediately after being published; usually a considerable time is required during which the chemical world assimilates the author's views in a more or less unconscious manner, until some day they find their way into textbooks. It is a remarkable tribute to the value of Thiele's theory that it became a classic almost as soon as it was published.

The Thiele theory[1] is based upon the following assumption: In the case of a double bond between two atoms, it is supposed that the whole of the affinity of the atoms is not used up, but that in addition to the attractive force which is utilized in joining the two atoms together there is a slight excess on each atom. This slight excess of valency Thiele designates by the name *Partial Valency,* and to its presence he attributes the additive power which unsaturated compounds display. To represent the partial valencies, Thiele employs a dotted line, thus—

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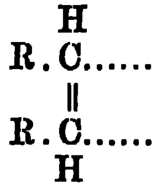
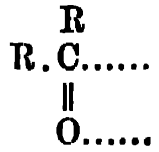
* The ozonides are explosive substances.

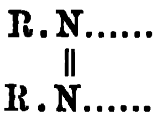
[1] Thiele, *Annalen*, 1899, 306, 87.



$$\begin{array}{c} \mathrm{H} \\ \mathrm{R.C}\ldots\ldots \\ \| \\ \mathrm{R.C}\ldots\ldots \\ \mathrm{H} \end{array}$$



$$\begin{array}{c} \mathrm{R} \\ \mathrm{R.C}\ldots\ldots \\ \| \\ \mathrm{O}\ldots\ldots \end{array}$$



$$\begin{array}{c} \mathrm{R.N}\ldots\ldots \\ \| \\ \mathrm{R.N}\ldots\ldots \end{array}$$

Now, when we come to the consideration of such a system as

$$\mathrm{R.CH:CH.CH:CH.R}$$

we find that it shows one peculiar property in connection with addition reactions. Since it contains two double bonds, it might be expected to take up four atoms of hydrogen or bromine at once, or at least to take up two atoms of bromine or hydrogen at one of the double bonds. In other words, we should expect to find one molecule of bromine attacking it first with the formation of the compound—

$$\mathrm{R.CHBr.CHBr.CH:CH.R}$$

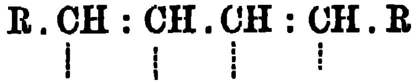
to which another bromine molecule might be added, giving the tetrabromo-compound—

$$\mathrm{R.CHBr.CHBr.CHBr.CHBr.R}$$

In practice, however, the first molecule of bromine does not attack either of the double bonds; it attacks them both at once, with the formation of the compound—

$$\mathrm{R.CHBr.CH:CH.CHBr.R}$$

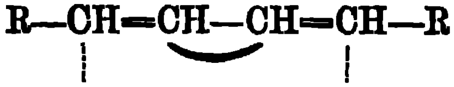
in which both of the original double bonds have disappeared, while a new double bond has been formed in the centre of the molecule. If we write out the scheme of partial valencies for the original substance—



$$\begin{array}{l} \mathrm{R.CH:CH.CH:CH.R} \\ \quad\;\, \vdots \quad\;\; \vdots \quad\;\; \vdots \quad\;\; \vdots \end{array}$$

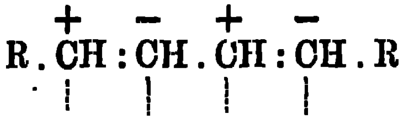
it is evident that only the two at the ends of the system have the faculty of attracting bromine, the two middle partial valencies failing to act. In order to express this behaviour

Thiele writes the formula in the following way, in which the two central partial valencies are supposed to have neutralized one other:—

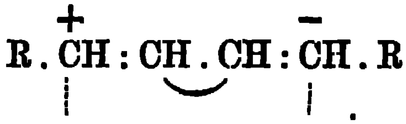


$$\mathrm{R{-}\underset{\vdots}{CH}{=}\underbrace{CH{-}CH}{=}\underset{\vdots}{CH}{-}R}$$

We can symbolize this behaviour by supposing that the carbon atoms of the chain are charged alternately with positive and negative forces; the two central atoms will then neutralize one another, leaving the ends still charged—



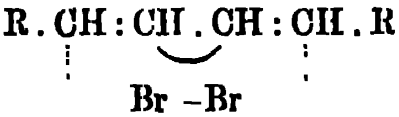
$$\mathrm{R.\underset{\vdots}{\overset{+}{CH}}:\underset{\vdots}{\overset{-}{CH}}.\underset{\vdots}{\overset{+}{CH}}:\underset{\vdots}{\overset{-}{CH}}.R}$$



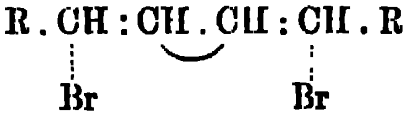
$$\mathrm{R.\underset{\vdots}{\overset{+}{CH}}:\underbrace{CH.CH}:\underset{\vdots}{\overset{-}{CH}}.R}$$

Such a system Thiele terms a *Conjugated Double Bond.*

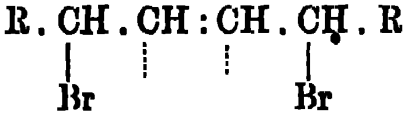
If addition takes place in the case of a conjugated double bond, obviously the two new atoms will attach themselves at the ends of the chain in the position indicated by the free partial valencies. But this does not end the matter: for no sooner has addition taken place than the conjugation is destroyed; and hence a new double bond will be formed between the central atoms of the system—



$$\mathrm{R.\underset{\vdots}{CH}:\underbrace{CH.CH}_{Br\ -Br}:\underset{\vdots}{CH}.R}$$

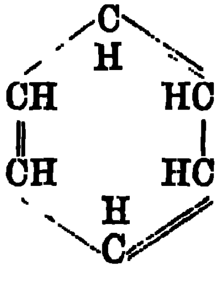


$$\mathrm{R.\underset{\substack{\vdots\\Br}}{CH}:\underbrace{CH.CH}:\underset{\substack{\vdots\\Br}}{CH}.R}$$

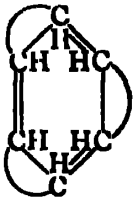


$$\mathrm{R.\underset{\substack{|\\Br}}{CH}.\underset{\vdots}{CH}:\underset{\vdots}{CH}.\underset{\substack{|\\Br}}{CH}.R}$$

The most striking application of the Thiele theory, however, is found in the case of the benzene ring. If we write down the Kekulé formula for benzene, and fill in the partial valencies in the usual way, we arrive at the following figure:—



An examination of this system will show that it forms *a closed series of conjugated double bonds.* In other words, it can be written as shown below, and no free partial valencies exist in the system. Thus an explanation is furnished for the impossibility of producing addition products with benzene under ordinary conditions.



Though the theory of partial valencies has very widespread application, it is not absolutely accurate; for several cases are known in which it is not in accordance with the results of experiment.[1]

As far as the benzene nucleus is concerned, the question which has excited most interest recently is the orientation of substituents in the ring. For example, when chlorobenzene is nitrated, a mixture of ortho- and para-chloro-nitrobenzenes is formed; whereas when nitrobenzene is chlorinated the product is mainly meta-chloro-nitrobenzene. Thus when the chlorine atom is the original substituent it "directs" the entering group into the ortho- and para-positions; whereas if the nitro-group be originally present it influences the entering substituent towards the meta-position. The only simple rule formulated so far has been that suggested by Crum Brown and Gibson,[2] which may be stated as follows. Write down the formula for the mono-substituted benzene compound which is to be further acted upon. In this formula replace C_6H_5 by H. If this new compound can be oxidized *directly* to a higher stage of oxidation, then a meta-derivative will result from further substitution of the original benzene compound; but if no such direct oxidation of the hydrogen compound is possible, then ortho- and para-derivatives will be formed as the main products in further substitution. For example, take the cases given above. If we start with $C_6H_5.NO_2$ and replace the phenyl radicle by a hydrogen atom, we get HNO_2. Nitrous acid can be oxidized to nitric acid easily. Whence according to the rule, a second substituent entering the nitrobenzene nucleus will go into the meta-position. On the other hand, if chlorobenzene be our starting-point, the hydrogen compound will be hydrochloric acid; and as this is not oxidizable directly to hypochlorous acid, the rule indicates that a mixture of ortho- and para-derivatives will be formed when a second substituent enters the chlorobenzene nucleus.

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[1] Harries, *Annalen*, 1903, 330, 185; Bredt and Kallen, *ibid.*, 293, 338.

[2] Crum Brown and Gibson, *Trans.*, 1892, 61, 367.

When more complex cases are examined, the factors governing the orientation of the entering substituents become much more complex; and as the Crum Brown and Gibson rule itself is not without certain exceptions, it will be seen that the problem is by no means a simple one.[1]

Passing to other subjects, intramolecular change must be mentioned, as in this region much work of first-class importance has been carried out since the beginning of the century. It would lead us too far were we to enter into any general discussion of the problem; but one or two examples must be given.

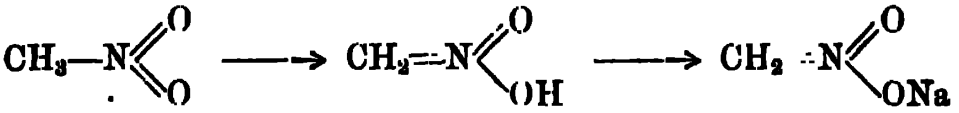
The most striking of these is the discovery by Hantzsch of a new class of electrolytes which have been named pseudo-acids and pseudo-bases. Previous to his work, the electrolytes known to us might be grouped under the four following heads: (1) Acids, which give rise to hydrogen ions; (2) Bases, which yield hydroxyl ions; (3) Salts, which dissociate into acidic and basic ions; and (4) Amphoteric electrolytes, which are capable of producing either hydrogen or hydroxyl ions according to the experimental conditions employed.

Now when an acid solution is neutralized by means of a base, the solution is acidic at the beginning and remains acidic all through the titration until the neutralization-point is reached. On the other hand, if we start with a solution of nitromethane, it is neutral in reaction; and yet if we slowly add to it a solution of sodium hydroxide, the solution does not become alkaline at once. In fact, we may have to add a considerable quantity of alkali before the next drop produces an alkaline reaction in the liquid. Clearly nitromethane is a neutral substance which, *given time*, can exhibit acidic properties in presence of alkali. It is this *slow neutralization* which distinguishes it from a true acid.

---

[1] For full information on the subject, see Holleman, *Die direkte Einführung von Substituenten in den Benzolkern* (1910), and Obermiller, *Die orientierenden Einflüsse und der Benzolkern* (1909).

Without going into the details of the evidence, it may be said that intramolecular change is the governing factor in the problem. True nitromethane is not acidic; but in presence of bases it may change into an isomeric body, the *aci*-form, which possesses a hydrogen capable of being replaced by alkali: so that the reaction may be represented by the following scheme:—



$$CH_3{-}N{\overset{O}{\underset{O}{\lessgtr}}} \longrightarrow CH_2{=}N{\overset{O}{\underset{OH}{\lessgtr}}} \longrightarrow CH_2{=}N{\overset{O}{\underset{ONa}{\lessgtr}}}$$

Normal form. Aci-form. Salt.

The slowness with which nitromethane neutralizes alkalies is obviously due to the fact that the intramolecular change from the normal to the aci-form is not instantaneous, but requires time for its accomplishment.

The discovery of the pseudo-acids resulted in the collapse of Ostwald's hypothesis as to the nature of indicators. Ostwald[1] assumed that indicators underwent a change of colour when dissociated into their ions. Thus undissociated phenolphthalein, in his view, was colourless; but when converted into the easily dissociable sodium salt it broke down into ions which were red in colour. By adding acid to the alkaline solution, the dissociation of the phenolphthalein was restricted; and hence the colour disappeared. Stieglitz[2] suggested, on the other hand, that the production of the colour was due to intramolecular change in the phenolphthalein molecule; and Hantzsch[3] confirmed this, showing that phenolphthalein, for example, changes from the benzenoid to the quinonoid structure under the influence of alkali, and on further addition of alkali gives a *colourless* solution, a fact which cannot be explained by Ostwald's hypothesis.[4]

---

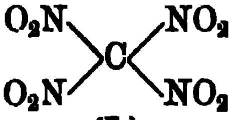
[1] Ostwald, *Die wissenschaftlichen Grundlagen der analytischen Chemie* (1894).

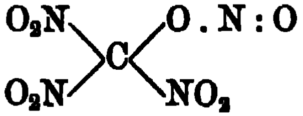
[2] Stieglitz, *J. Amer. Chem. Soc.*, 1903, **25**, 112.

[3] Hantzsch, *Ber.*, 1906, **39**, 1090.

[4] It is perhaps not without interest to note that Ostwald in his *Grundriss der allgemeinen Chemie* (1912) still gives his hypothesis as the correct one—a curious example of incapacity to grasp the bearing of organic problems.

In connection with intramolecular change the case of tetranitromethane may be mentioned.[1] Under normal circumstances, this substance appears to exist in the pure "nitro" form (I.), but in presence of amines or alkyl sulphides it seems slowly to be converted into trinitro-nitrito-methane (II.), as it gives exactly the same colour reactions as are observed in the case of alkyl nitrites:—


(I.)

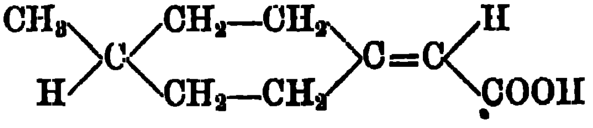

(II.)

This case seems to be a halfway stage towards pseudo-acid formation.

At this point the progress in stereochemistry during the present century may be conveniently described. It must be confessed that though the period opened with high hopes, these have not been fulfilled by the increase of interest in the subject.

In 1899 the only two elements known to be capable of forming asymmetric centres of optical activity were carbon and nitrogen; but since then the list has been greatly increased by the addition of sulphur,[2] selenium,[3] tin,[4] silicon,[5] phosphorus,[6] cobalt,[7] chromium,[8] rhodium,[9] and iron.[10]

The whole question of molecular symmetry was raised by a paper of Perkin, Pope, and Wallach[11] describing the resolution into optically active components of an acid having the following structure:—



It will be recalled that in one of his earliest publications on stereochemistry, van't Hoff pointed out that optical activity might be expected in compounds of the type—

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[1] Harper and Macbeth, *Trans.*, 1915, **107**, 87; Macbeth, *ibid.*, 1824.

[2] Smiles, *Trans.*, 1900, **77**, 1174; Pope and Peachey, *ibid.*, 1072.

[3] Pope and Neville, *Trans.*, 1900, **81**, 1552.

[4] Pope and Peachey, *Proc.*, 1900, **16**, 42, 116.

[5] Kipping, *Trans.*, 1907, **91**, 209.

[6] Kipping and Challenger, *Trans.*, 1911, **99**, 626; Meisenheimer and Lichtenstadt, *Ber.*, 1911, **44**, 356.

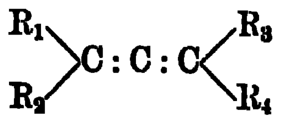
[7] Werner, *Ber.*, 1911, **44**, 1887.

[8] *Ibid.*, 3231.

[9] *Ibid.*, 1912, **45**, 1228.

[10] *Ibid.*, 433.

[11] Perkin, Pope, and Wallach, *Trans.*, 1909, **95**, 1785; compare Perkin and Pope, *Trans.*, 1911, **99**, 1510.



$R_1R_2C:C:CR_3R_4$

owing to the fact that, although there is no asymmetric carbon atom in the molecule, the groups R_1, R_2, R_3, and R_4 are tetrahedrally grouped in space, as can easily be seen by considering the arrangement of bonds around the central carbon atom on the van't Hoff hypothesis. The one double bond lies in the plane of the paper, whilst the other must be at right angles to the paper; and hence a similar grouping of R_1 and R_2 in the plane of the paper and R_3 and R_4 above the plane of the paper must exist. The cyclic compound shown above belongs to the same type, since in its case the ring takes the place of one of the double bonds.

The claim that this substance contained no asymmetric carbon atom was contested[1] on the ground that the carbon atom carrying the methyl group is really asymmetrical if the structure of the rest of the molecule be taken into consideration. The matter seems to be one depending upon the interpretation given to the term "asymmetric carbon atom"; and the reader may form his own judgment on the question.

New methods of resolving racemic compounds into their antipodes have been devised. Some of these present nothing essentially novel in conception.[2]

Much more original was the method devised by Marckwald and Meth[3] which depends upon the difference in rapidity of amide formation between an active amine and the *d*- and *l*-forms of an active acid. Thus when racemic mandelic acid was heated with lævo-menthylamine, it was found that the acid left unacted upon after the process had gone on for ten hours was optically active. This method is based on the same line of reasoning as the method of Marckwald and McKenzie[4] who showed that when racemic mandelic acid is esterified with menthol the reaction between the menthol and the *d*-form is more rapid than is the case with the *l*-acid; so that by interrupting the process before the acid is completely esterified the residual acid is optically active.

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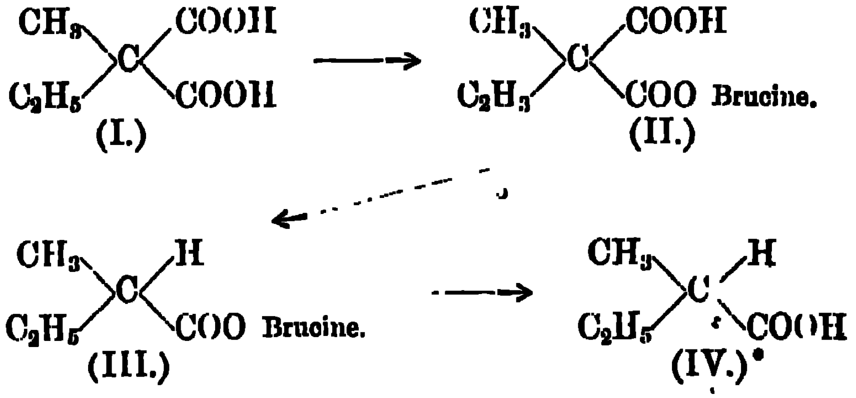
[1] Everest, *Chem. News*, 1909, **100**, 295; *Proc.*, 1911, **27**, 285; Marsh, *Proc.*, 1911, **27**, 317.

[2] Erlenmeyer, jun., *Ber.*, 1903, **36**, 976; Neuberg, *Ber.*, 1903, **36**, 1192.

[3] Marckwald and Meth, *Ber.*, 1905, **38**, 801.

[4] Marckwald and McKenzie, *Ber.*, 1899, **32**, 2130.

A fresh field was opened up by Marckwald[1] in the accomplishment of the first asymmetric synthesis of an optically active substance. In an asymmetric synthesis, an optically active compound is taken as the starting-point. To this an extra radicle is added, so as to form a new asymmetric carbon atom. The original optically active portion of the molecule is then split off; and if the synthesis is successful, the remainder of the substance, containing the new asymmetric carbon atom, will be optically active. For example, Marckwald utilized methyl-ethyl-malonic acid (I.) which contains no asymmetric carbon atom. He combined this with optically active brucine, thus introducing asymmetry into the molecule (II.). Now on heating this compound, carbon dioxide is split off forming (III.), a compound which contains a new asymmetric carbon atom. Under the influence of the active brucine, a preference is given to one active form over the other during this process; and when the brucine is split off again, the acid



remaining (IV.) is found to be optically active.

In the whole field of stereochemistry, no more puzzling phenomena are known than those grouped under the head of the Walden Inversion; and at the present day we still await a solution of the problem. The data are so complicated that it would be impossible to deal with them fully here: all that can be done is to indicate the nature of the question.[2]

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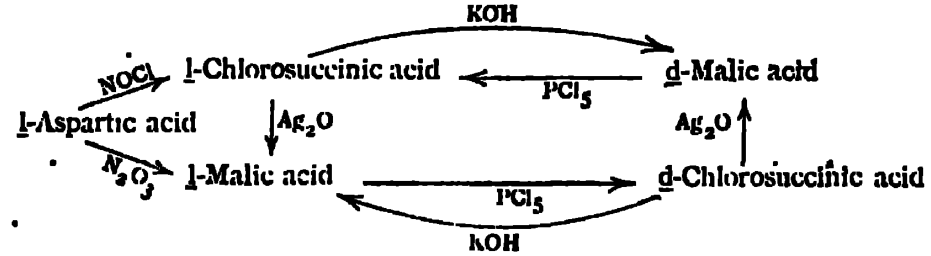
[1] Marckwald, *Ber.*, 1904, 37, 349, 1368, 4696.

[2] For further details and references, see *Chem. Soc. Ann. Reports*, 1911, 1912, and Stewart, *Stereochemistry* (2nd edition).

Walden[1] observed that when certain optically active compounds were treated with non-asymmetrical reagents the sign of the rotatory power was altered in some cases, dextro compounds being converted into lævo-isomers without any marked racemization being observed. The following scheme shows some of these conversions; and it will be seen that lævo-malic acid, for instance, can be changed into dextro-malic acid by the successive use of phosphorus pentachloride and silver oxide; whilst the converse change of dextro-malic acid into the lævo-isomer can be accomplished by the use of the same reagents in the same order:—



Another mysterious case is that of dextro-alanine and its ester.[2] When *d*-alanine is treated with nitrosyl bromide, it produces *l*-*α*-bromopropionic acid; whilst *d*-alanine ester, when subjected to the action of nitrosyl bromide and subsequent hydrolysis, yields the corresponding antipode, *d*-*α*-bromopropionic acid:—

Dextro-alanine $NH_2.CH(CH_3).COOH \xrightarrow{NOBr}$ Lævo-α-propionic acid.

Dextro-alanine ester $NH_2.CH(CH_3).COOEt \xrightarrow[\text{hydrolysis}]{\text{NOBr and}}$ Dextro-α-propionic acid.

Again, when silver oxide acts upon an *α*-halogen fatty acid and upon the product obtained by coupling this acid with glycine,[3] the results are optically different:—

$l\text{—}CH_3.CHBr.COOH \xrightarrow{Ag_2O} d\text{-}CH_3.CH(OH).COOH$

$l\text{—}CH_3.CHBr.CO.NH.CH_2.COOH \xrightarrow{Ag_2O\text{ and hydrolysis}} l\text{-}CH_3.CH(OH).COOH$

Finally, the case of *l*-*α*-hydroxy-*α*-phenylpropionic acid may be mentioned.[1] When this substance is treated with phosphorus pentachloride it yields a *d*-chloro-acid; whilst when thionyl chloride is used, there is no change of rotatory power, the *l*-chloro-acid being formed :—

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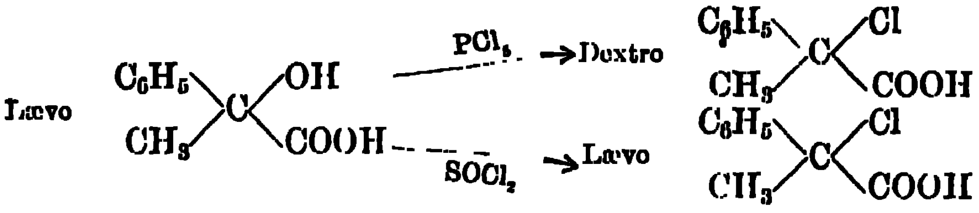
[1] Walden, *Ber.*, 1893, **26**, 213; 1895, **28**, 1287, 2771; 1897, **30**, 3146; 1899, **32**, 1833, 1855.

[2] Fischer, *Ber.*, 1907, **40**, 489.

[3] *Ibid.*, 502; Fischer and Raske, *ibid.*, 1052; Fischer and Schoeller, *Annalen*, 1907, **357**, 11.



Senter and his collaborators[2] have thrown light upon the matter from a different direction by examining the influence of the solvent on the course of the reaction. In the case of optically active bromophenylacetic acid, $C_6H_5 . CHBr . COOH$, they have shown that if this be allowed to react with ammonia in aqueous or alcoholic solution, the amino-acid formed has a sign opposite to that of the original bromo-compound; whilst if the solvent be liquid ammonia or acetonitrile, the sign of the rotatory power is not reversed by the reaction. Imino-diphenylacetic acid is formed to some extent during the reaction. When α-bromo-β-phenylpropionic acid, $C_6H_5 . CH_2 . CHBr . COOH$, is treated with ammonia in various solvents, some cinnamic acid is always produced.

One of the most complicated problems in the stereochemical field is that which concerns the numerical value of optical rotatory power. Two subsidiary questions are here involved: first, the influence of the active compound's structure; and second, the effect of the solvent in which it may be dissolved. With regard to the first of these we are still apparently far from any satisfactory conclusion, though many facts have been accumulated by various investigators. Certain rough generalizations with regard to the effect of introducing double or triple bonds in place of single linkages have been made; but we are still far from the time when it may be possible to assess the approximate numerical value of the rotatory power from an examination of the active compound's constitution, as we can do in the case of refractive indices.

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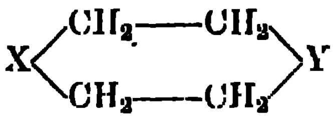
[1] Mackenzie and Clough, *Trans.*, 1910, 97, 1016, 2566.

[2] Senter and Drew, *Trans.*, 1915, 107, 638; 1916, 109, 1091; Senter and Tucker, *Trans.*, 1918, 113, 140; Senter, Drew, and Martin, *ibid.*, 151.

Another problem which has attracted a certain amount of attention in recent times is concerned with what has been termed spatial conjugation. It will be recalled that on the hypothesis of the tetrahedral arrangement of groups around the carbon atom, the first carbon atom in a straight chain may approximate closely in space to the fifth and sixth atoms of the chain. Similarly it is assumed on account of various reactions that the 1:4 positions of a six-membered cyclic compound may also be in some way closely related to each other. From an examination of optically active salts and esters of dicarboxylic acids in which the carboxyl radicles lay at opposite ends of the chain, Hilditch[1] showed that when these groups were situated in the 1:5 or 1:6 positions with regard to one another anomalous rotatory powers were observed; from which it follows that the groups must have influenced one another owing to their proximity in space, since structurally they are far removed from each other.

The same problem was attacked in a different way by Clarke.[2] He measured the reactivity of atoms in the positions X and Y in the formula below, wherein X and Y may be $=NR$, $-O-$ and $-S-$. All possible combinations of these groups in pairs were investigated:—



It was found that when X and Y are atoms capable of raising their valency (for example: divalent sulphur, which can become quadrivalent, or trivalent nitrogen, which can show pentavalence) and may therefore be supposed to be capable of exhibiting residual affinity, the two atoms X and Y do actually influence each other's reactivities. Further, if X and Y be identical, their reactive power is increased; whereas if X and Y be different (for example $X = S$ and $Y = O$) their reactivity is diminished.

A fresh aspect of the question is disclosed when the absorption spectra of stereoisomerides are examined.[3] Since these compounds are structurally identical, the difference in their absorptive power must be ascribed to purely spatial influences. It was found that the difference between the absorption spectra of two isomerides was greatest when the change from one form to the other entailed the relative shifting in space of two unsaturated radicles. When this condition was not present the differences observed were slight.

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[1] Hilditch, *Trans.*, 1909, **95**, 1578.

[2] Clarke, *Trans.*, 1912, **101**, 1788.

[3] Macbeth, Stewart, and Wright, *Trans.*, 1912, **101**, 599.

These pieces of evidence, drawn from such widely differing fields, certainly point to the probability that spatial conjugation is a factor which may play a marked part in certain cases.

We now come to a subject which lies in the borderland between organic and physical chemistry, namely, the relations between the physical properties of compounds and their chemical structure.[1] The problems comprised in this branch have, for the most part, been solved by organic chemists, owing to the fact that the material of experiment is largely drawn from the carbon compounds. The curious step-motherly fashion in which this important subject has been treated by the ordinary physical chemist is possibly due to the influence of Ostwald, who had a large following among the older group of physical chemists; or it may be ascribed to the fact that few physical chemists have any claim to be ranked as even moderate organic chemists, a fact which handicaps them in this particular line of research. Whatever be the reason, there is no doubt that the relations between chemical constitution and physical properties, so fully recognized by van't Hoff, have not been pursued with either eagerness or success by the physical chemists of the Ostwald school.

Surface tension, specific heat, boiling-point, and melting-point have occupied less attention in recent years. The influence of chemical structure upon viscosity has furnished a subject for a number of workers, among whom Dunstan and his collaborators have been the most successful. The relations between volume and valency have formed the basis of a considerable amount of ingenious speculation by Traube, Barlow and Pope, and Le Bas. The main trend of research, however, has been towards the study of optical properties.

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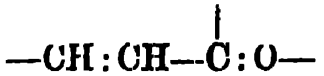
[1] For a complete account of this field up to 1910, the reader should consult Smiles' *Relations between Chemical Constitution and some Physical Properties.* Even a cursory perusal of the book will suggest many subjects for further investigation.

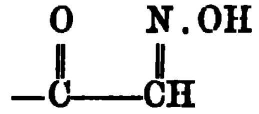
The physical properties of a molecule may be regarded from either of two different standpoints: for we may assume the molecular properties to be merely the sum of the properties of the various atoms in the molecule; or we may decide to lay most weight upon the structural character of the compound. Unfortunately, this mode of classification breaks down at certain points; for it is found that in the case of some substances the properties of the molecule are apparently compounded partly from purely additive factors and partly from constitutive effects. A certain physical property may be traced as an additive factor throughout a whole series of compounds, and then may finally be so greatly influenced by constitutive factors that the value deduced from additive methods diverges widely from the result of experiment upon the next member of the series. Thus when we speak of additive and constitutive properties we mean merely that in the one case the additive factor is predominant, whilst in the second case the influence of constitution outweighs the purely additive effects.

Refractive index gives an example of this. In the case of saturated molecules or unsaturated compounds containing a single centre of residual affinity, the refractivity of the substance can be calculated with extraordinary accuracy by adding together the refractivities of the atoms contained in it. But if the molecule contains a conjugated system* of double bonds such as

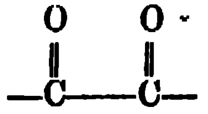
$—CH:CH—CH:CH—$



$—CH:CH—\overset{|}{C}:O—$



$\overset{\overset{\textstyle O}{\|}}{—C}———\overset{\overset{\textstyle N.OH}{\|}}{CH}$



$\overset{\overset{\textstyle O}{\|}}{—C}———\overset{\overset{\textstyle O}{\|}}{C}—$

the refractivity becomes anomalous and cannot be calculated from the separate refractivities of the atoms. In this case it is clear that constitutive influences are overbearing the purely additive relationship.

Magnetic rotatory power—*i.e.* the power of rotating the plane of polarization which is acquired by symmetrical substances placed in a strong magnetic field—closely resembles refractivity in this respect. Substances containing conjugated double bonds exhibit a certain "exaltation" above the calculated rotatory power; so that here also the influence of the constitutional factor outweighs the additive effects.

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* See p. 12.

Magnetic susceptibility[1] has recently been studied from the constitutional standpoint, and it is found to resemble magnetic rotatory power in character, being influenced partly by additive factors and partly by the general constitution of the molecular structure.

When absorption spectra are examined, it is found that the additive factor is completely overborne, and that the manner in which the atoms are linked together in the molecule exerts far more influence than the nature of the atoms themselves. In recent times this subject has attracted very wide interest, either in the crude form of "relations between colour and constitution" or in the more accurate survey of the visible and ultra-violet regions by the aid of the quartz spectrograph; and within the last few years the work of Henri[2] has opened up the possibility of calculating the graphs of compounds from data obtained by the examination of typical substances.

Another physical property which appears to be of value in ascertaining the presence or absence of a hydroxyl radicle, is anomalous electric absorption, which was first noticed by Drude.[3] It is found that hydroxylic substances strongly absorb Herzian waves; and this faculty enables enolic forms to be recognized in certain cases.

Electrical double refraction has also been worked upon, but from the results in this case the property appears to be so highly constitutive in character that it varies with very slight changes of structure; so that it is impossible at present to find any way of co-ordinating the numerical results with the chemical side.

The luminescence of certain organic vapours when subjected to the action of a current passing in a solenoid has been studied by Kauffmann in the hope of throwing some light upon the fluorescence problem; but the whole matter of the relation between fluorescence and chemical constitution is still but little understood.

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[1] Pascal, *Bull. soc. chim.*, 1909 (iv.), 5, 1110.

[2] Henri, *Études de photochimie*, 1919.

[3] Drude, *Zeitsch. physikal. Chem.*, 1902, 40, 635: compare Walden, *ibid.*, 1903, 46, 176.

From the foregoing paragraphs it will be seen that an immense amount of research remains to be done upon the connection between physical properties and chemical structure. We still await some general theory which will co-ordinate the various branches of the subject. From a survey of the data at present available, it seems clear that the more purely electrical a property is, the more does the influence of constitution preponderate. Thus refractive index is largely additive; magnetic rotation and magnetic susceptibility are slightly more constitutive in character; anomalous electric absorption and electrical double refraction are almost entirely constitutive properties. It is true that absorption spectra form an apparent exception to this rule.

Photochemistry[1] has grown by leaps and bounds since the beginning of the century and is rapidly reaching the stage when it will be considered a subject in itself. The problems already presented by it are too numerous to be dealt with in this place; and yet the fringe of the subject is all that has been attacked as yet.

The survey given in the previous pages of the progress of organic chemistry during the present century, though very incomplete, will suffice to indicate the main lines upon which work is proceeding at the present day; and it should be sufficient to show that fresh subjects of research are still plentiful. The newer trend towards a study of natural products comes as a relief after the long supremacy of the purely synthetic work of the late nineteenth century; and it may be emphasized in this place that in the near future the study of quite simple reactions will offer many points of interest. We are far too apt to be captivated by the application of old reactions to new syntheses; and it seems likely that more interesting and useful work could be carried out by an examination of even such obvious problems as the hydration and dehydration of simple organic compounds.

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[1] A full account of the subject is given in Sheppard's *Photochemistry* (1914).

CHAPTER II

THE MONO-CYCLIC TERPENES

1. *Introductory.*

When the saps and tissues of certain plants (such as pines, camphor, lemons, and thyme) are distilled, the distillates are found to contain among other things a mixture of substances which are classed under the general head of ethereal oils. For the most part these ethereal oils contain unsaturated hydrocarbons of the general formula $(C_5H_8)_n$ (or derivatives of these substances), and these may be divided into three classes—

1. Open-chain olefinic compounds.
2. Mono-cyclic hydrocarbons (reduced benzene derivatives).
3. Cyclic compounds containing more than one ring.

In the naturally occurring compounds it is found that by far the greater number of these hydrocarbons have the empirical formula $C_{10}H_{16}$, and it is not without interest that Collie,[1] in polymerizing ethylene by means of the silent electric discharge, found that the major part of the substance used was converted into compounds containing either ten or fifteen carbon atoms.

The nomenclature of these substances is at present somewhat in confusion. It has been customary to apply the name terpene to any compound having the composition C_5H_8, or any polymeric variety of this type. This general type was then divided into two others: the "true terpenes," cyclic substances of the formula $C_{10}H_{16}$; and the "olefinic terpenes," which are open-chain bodies having the formulæ C_5H_8 and $C_{10}H_{16}$. Another system of nomenclature classes the whole group under three heads: hemi-terpenes, C_5H_8; terpenes, $C_{10}H_{16}$; and sesqui-terpenes, $C_{15}H_{24}$. The naturally occurring mono-cyclic terpenes are for the most part derived from either *m*- or *p*-hexahydrocymene.

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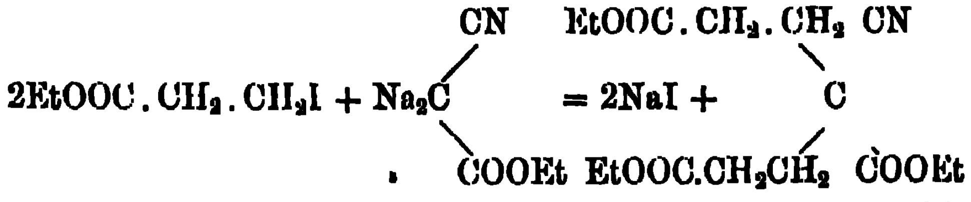
[1] Collie, *Trans. Chem. Soc.*, 1905, 87, 1540.

Most of the terpenes are colourless, pleasant-smelling liquids of high refractive power. They boil without decomposition, and are volatile in steam. Some are optically active, some inactive by racemization, while others, containing no asymmetric carbon atom, cannot show activity at all.

2. *The Synthesis of Terpineol.*

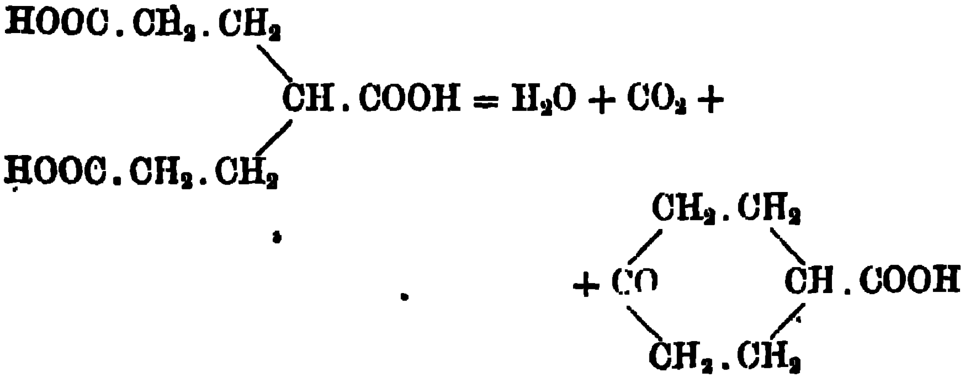
In the group of the mono-cyclic terpenes, by far the most important compound is terpineol, for from it most of the other members of the group can be prepared, either directly or indirectly. The constitution of terpineol, therefore, is of considerable value to us in determining the constitutions of other substances which we can derive from it. The inactive form of terpineol has been synthesized by Perkin,[1] and as this synthesis determines the constitution of the substance, we may describe it step by step.

When β-iodo-propionic ester was allowed to interact with the disodium derivative of cyan-acetic ester, γ-cyano-pentane-$\alpha\gamma\epsilon$-tricarboxylic ester was produced—



$$2\mathrm{EtOOC.CH_2.CH_2I} + \mathrm{Na_2}\overset{\diagup\,\mathrm{CN}}{\underset{\diagdown\,\mathrm{COOEt}}{\mathrm{C}}} = 2\mathrm{NaI} + \overset{\mathrm{EtOOC.CH_2.CH_2}\diagdown\quad\mathrm{CN}}{\underset{\mathrm{EtOOC.CH_2CH_2}\diagup\quad\mathrm{COOEt}}{\mathrm{C}}}$$

From this the free acid was obtained by hydrolysis with hydrochloric acid, and when it was boiled with acetic anhydride and then distilled, it was transformed by loss of water and carbon dioxide into δ-keto-hexahydrobenzoic acid—



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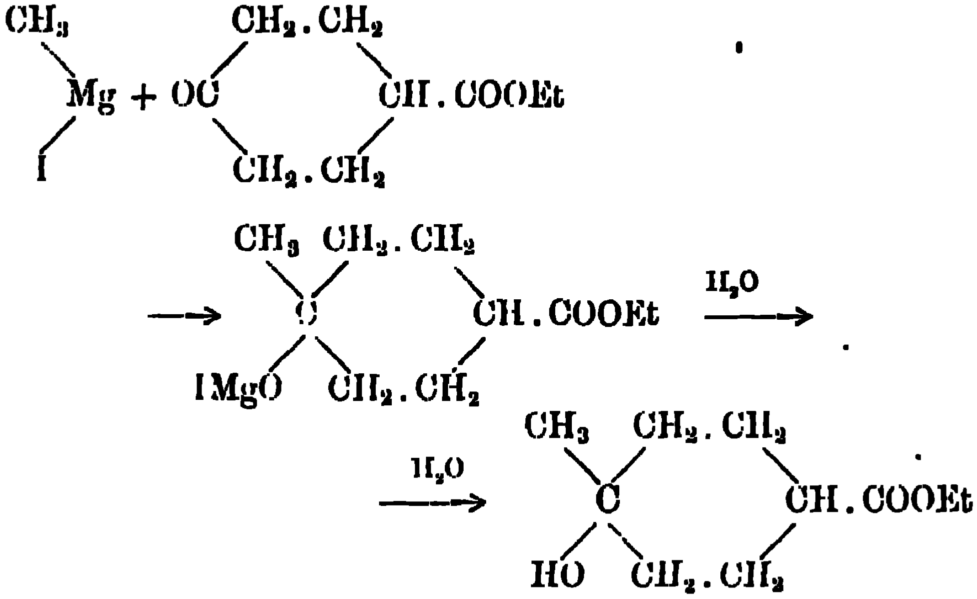
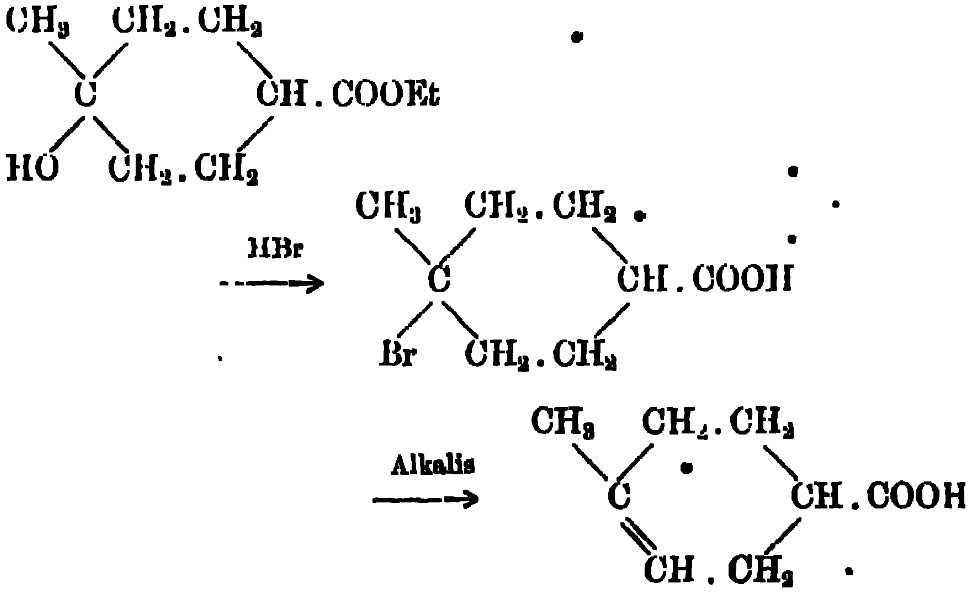
[1] Perkin, *Trans. Chem. Soc.*, 1904, 85, 64, 5.

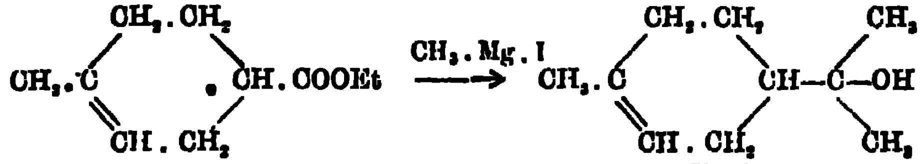
Grignard's reaction was then applied to the ester of this acid, magnesium methyl iodide being allowed to react with the ketonic group, and in this way δ-hydroxy-hexahydrotoluic ester was formed—



When, by the action of fuming hydrobromic acid, we replace the hydroxyl group in this acid by a bromine atom and then remove hydrobromic acid from the compound by means of weak alkalis or pyridine, we obtain Δ³-tetrahydro-p-toluic acid—



After esterifying the acid, the Grignard reaction can be again employed, with the result that the ester group is attacked, and on treatment with water the intermediate compound breaks down into inactive terpineol.



Terpineol.

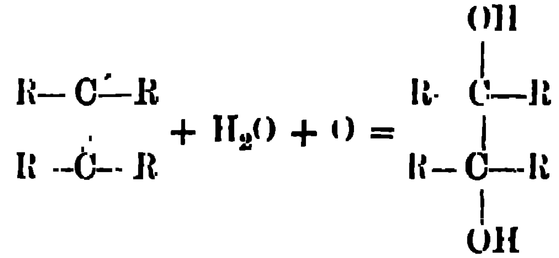
If this synthesis be examined step by step it will be seen that there can be no doubt as to the constitution of terpineol, for the reactions can only be supposed to take place in the way shown. Any alternative formulation of any of the reactions would at once lead to contradiction in the later experiments.

An optically active terpineol has been prepared by Fisher and Perkin[1] by resolving the intermediate acid into dextro and lævo forms before continuing the synthesis.

3. *The Decomposition Products of Terpineol.*

The oxidation of terpineol takes place in several steps and produces some compounds of importance in the study of terpene constitutions; we may, therefore, deal with the matter briefly in this place.

It has been shown by Wagner[2] that when a compound containing a double bond is oxidized by means of potassium permanganate, the first step in the process is the breaking of the double bond and the addition of a hydroxyl group to each of the atoms between which the double bond originally lay—



$$\begin{matrix} R-C-R \\ \| \\ R-C-R \end{matrix} + H_2O + O = \begin{matrix} & OH & \\ & | & \\ R- & C & -R \\ & | & \\ R- & C & -R \\ & | & \\ & OH & \end{matrix}$$

In the case of terpineol this rule holds, and it is found that the first oxidation product[3] obtained by the action of permanganate upon terpineol is trihydroxyhexahydrocymene—

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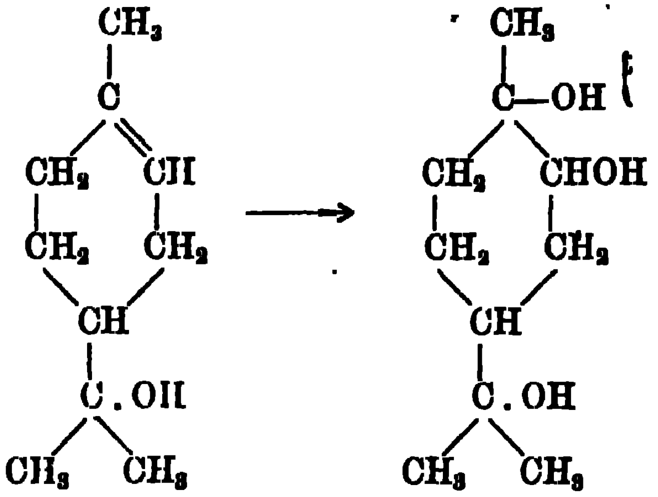
[1] Fisher and Perkin, *Trans. Chem. Soc.*, 1908, 93, 1871.

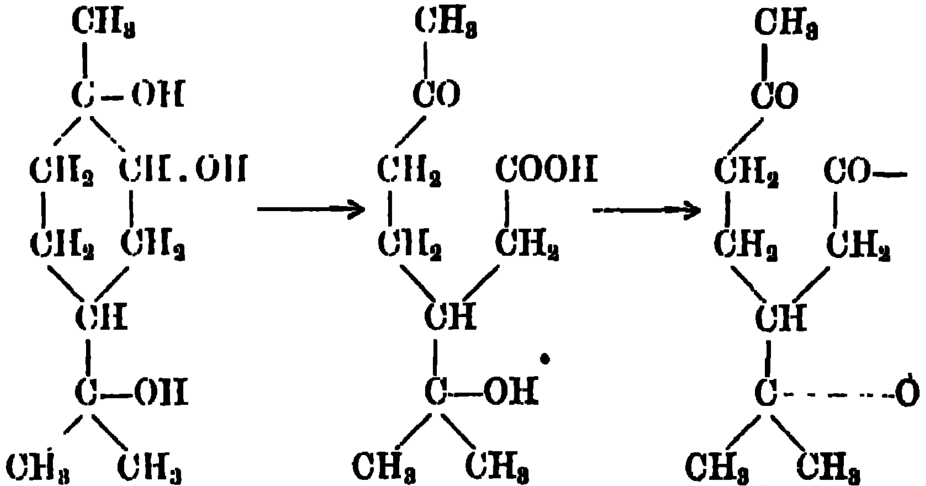
[2] Wagner, *Ber.*, 1888, 21, 1290, 3359; 1891, 24, 663.

[3] Wallach, *Annalen*, 1893, 275, 150.



Terpineol.   Trihydroxyhexahydrocymene.

This substance, on further oxidation,[1] is converted into homoterpenylic methyl ketone by the rupture of the single bond between the two hydroxyl-bearing carbon atoms—



Trihydroxyhexahydrocymene.   Intermediate acid.   Homoterpenylic methyl ketone.

As is shown in the formulæ, the first product of the oxidation is a hydroxy-acid which loses water at once between its carboxyl and hydroxyl groups, yielding the keto-lactone. This keto-lactone is the first product which can be isolated when terpineol is oxidized with chromic acid, for the action is so violent that the trihydroxyhexahydrocymene is destroyed as soon as it is formed.

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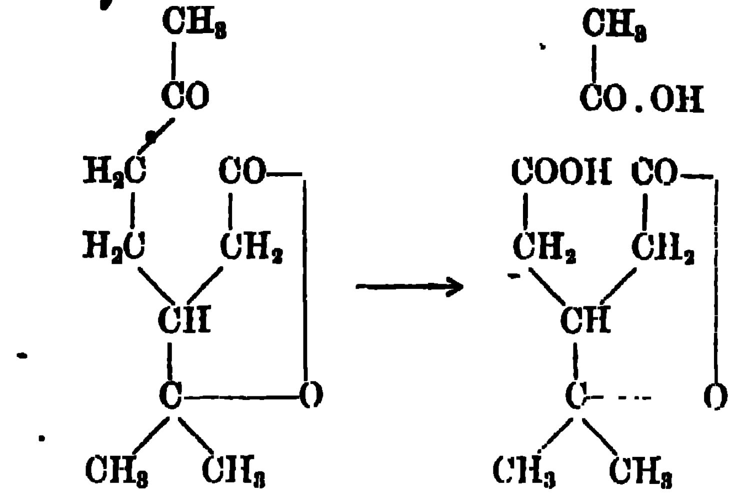
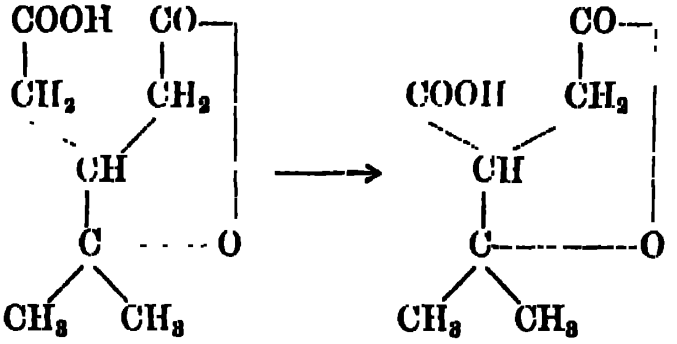
[1] Wallach, *Annalen*, 1893, 275, 150; *Ber.*, 1895, 28, 1773; Tiemann and Schmidt, *ibid.*, 1781.

Further oxidation with potassium permanganate[1] converts the keto-lactone into a mixture of acetic and terpenylic acids—



Homoterpenylic methyl ketone. Terpenylic acid.

The latter substance, by the action of a 5 per cent. solution of permanganate, is still further decomposed into terebic acid—



Terpenylic acid. Terebic acid.

It will be seen that these formulæ for homoterpenylic, terpenylic, and terebic acid illustrate the decomposition of terpineol quite satisfactorily. Any doubt as to their accuracy was removed by the synthesis of the three acids, which was carried out by Simonsen.[2] Terebic[3] and terpenylic acid[4] had previously been synthesized in different ways. The Simonsen syntheses depend on the application of Grignard's reaction to various ketonic esters. From magnesium methyl iodide and acetyl-succinic ester he obtained terebic ester—

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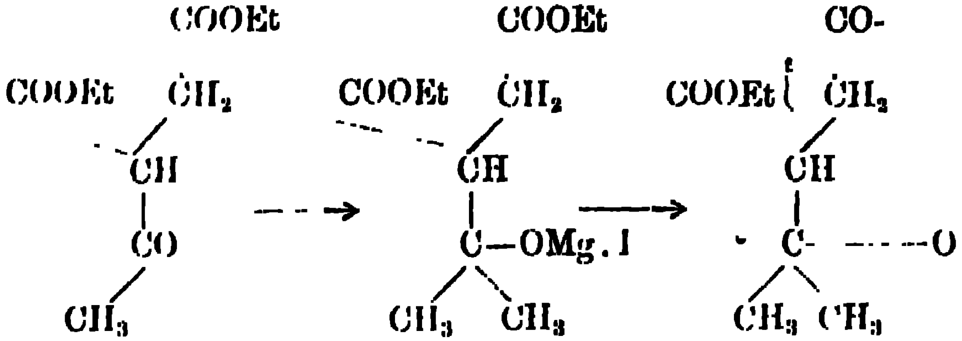
[1] Wallach, *Ber.*, 1895, 28, 1776.
[2] Simonsen, *Trans. Chem. Soc.*, 1907, 91, 184.
[3] Blaise, *C.R.*, 1898, 126, 349.
[4] Lawrence, *Trans. Chem. Soc.*, 1899, 75, 531.



Acetyl-succinic ester.

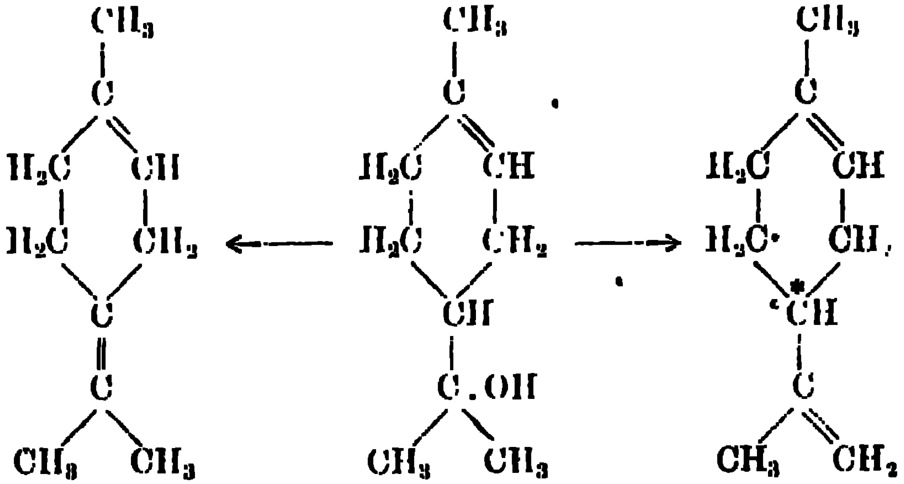
Terebic ester.

In exactly the same way β-acetyl-glutaric ester is converted into terpenylic ester, and β-acetyl-adipic ester into homoterpenylic ester.

The constitution of terpineol, then, may be considered to be completely established, both synthesis and degradation products agreeing with the theory.

4. *The Constitution of Dipentene.*

When terpineol is heated with acid potassium sulphate it loses a molecule of water, and is converted into dipentene. It is evident that we may represent this elimination of water in either of two ways—



(I.)

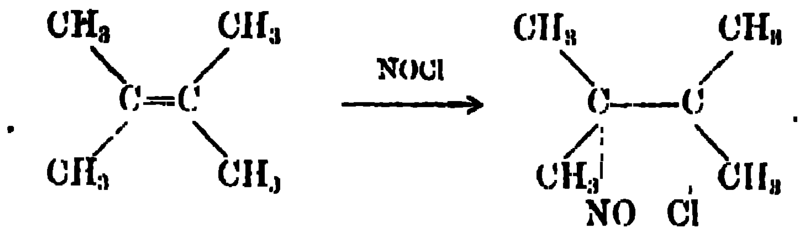
Terpineol.

(II.)

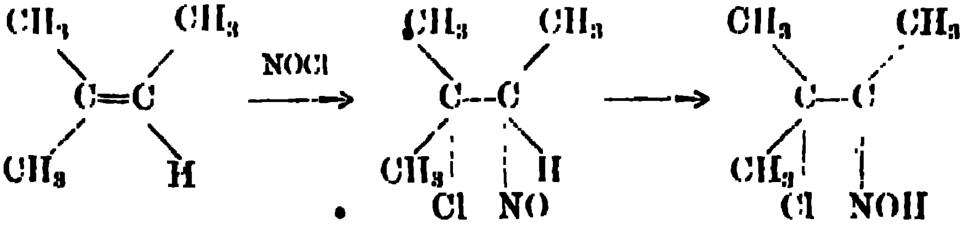
Now, dipentene can be obtained by mixing together equal quantities of dextro- and lævo-limonene. It is, therefore, the racemic form of limonene, and must contain an asymmetric carbon atom. Formula (I.) contains no such carbon atom, but the atom in (II.), which is marked with an asterisk, is asymmetric. Dipentene, then, must have the constitution represented by (II.).

In order to satisfy ourselves that this formula is the correct one, we may test it by seeing how far it agrees with some decompositions which dipentene can be made to undergo.

When nitrosyl chloride is allowed to act upon a compound containing a double bond it may unite with it in either of two ways.[1] If the double bond lies between two tertiary carbon atoms, the chlorine atom attaches itself to the one and the nitroso group to the other, and the resulting substance is a *blue* nitroso-derivative—



On the other hand, if one of the carbon atoms is a tertiary and the other a secondary one, the chlorine of the nitrosyl chloride attaches itself to the tertiary atom and the nitroso-group to the secondary atom. The hydrogen atom then wanders, as shown in the formulæ below, with the result that a *colourless iso*-nitroso-compound is formed—



We must now apply this to the case of dipentene. To make reference easy we shall number each step.

I. When nitrosyl chloride acts upon dipentene, it might be supposed that it could react either with the double bond in the nucleus or with that in the side-chain. It actually attacks the nuclear double bond, as we shall show later, and to avoid the complication of two sets of formulæ we may confine ourselves to the case of the addition to the double bond of the nucleus. The reaction, if our formula for dipentene be correct, will take the course shown below—

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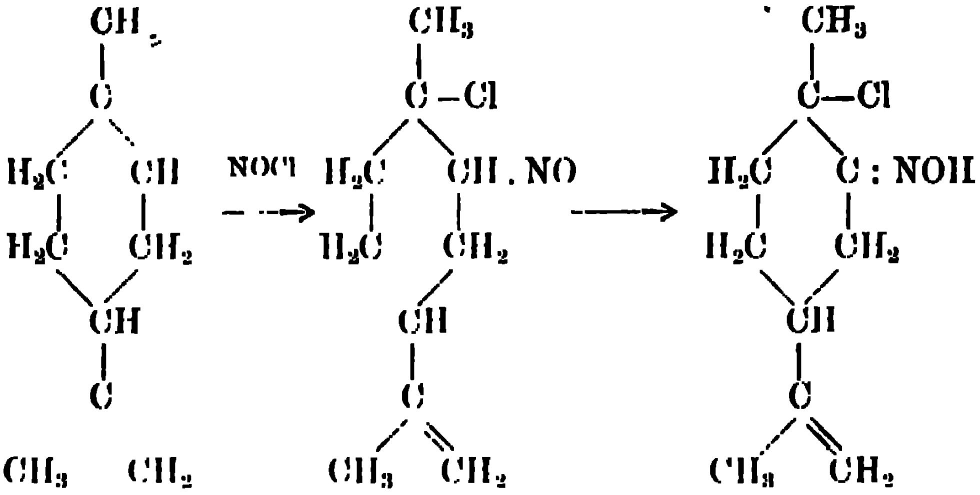
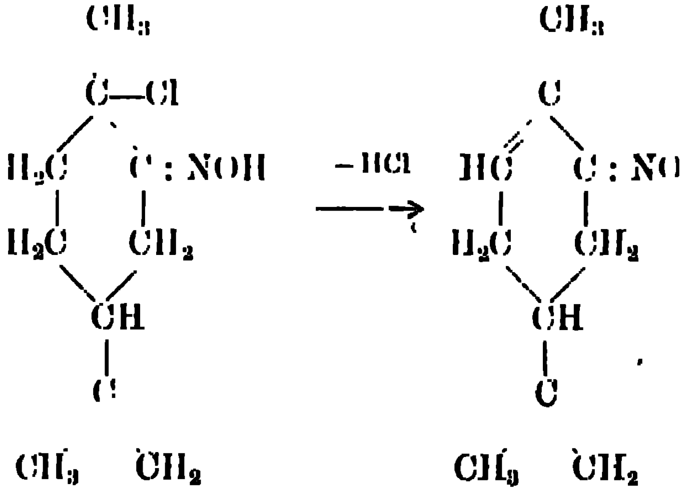
[1] Thiele, *Ber.*, 1894, 27, 455.



Dipentene.

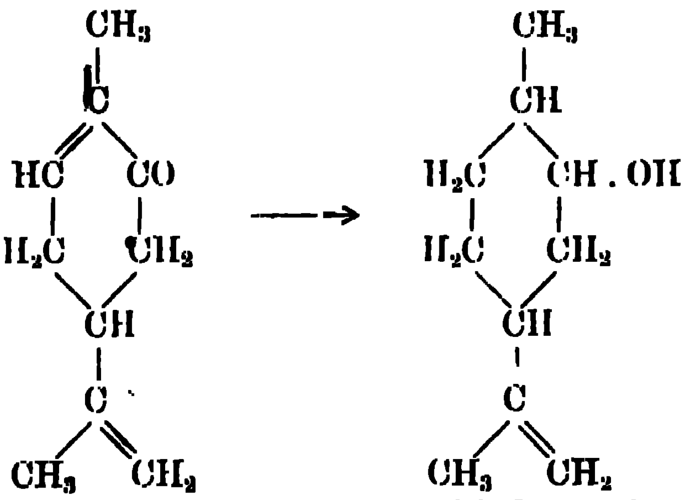
II. When the nitrosochloride formed in the last reaction is treated with alcoholic potash it loses one molecule of hydrochloric acid, and is transformed into a compound which proves to be identical with the oxime of the ketone carvone. This can be expressed as follows:—



Dipentene nitrosochloride. Carvoxime.

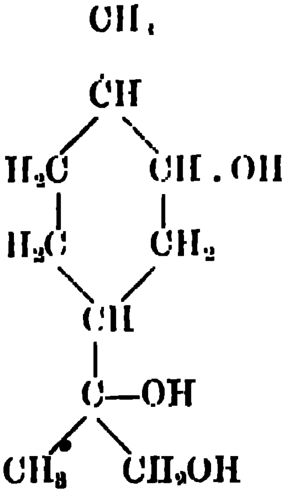
III. By hydrolysis of the oxime, carvone is produced.

IV. Carvone, on reduction, gives dihydrocarveol. This reduction might be supposed to take place either in the nucleus or in the side-chain. As will be shown later (VI.), the nucleus is reduced and the side-chain left untouched. We need not concern ourselves with the alternative set of formulæ, but may again confine ourselves to the one set—

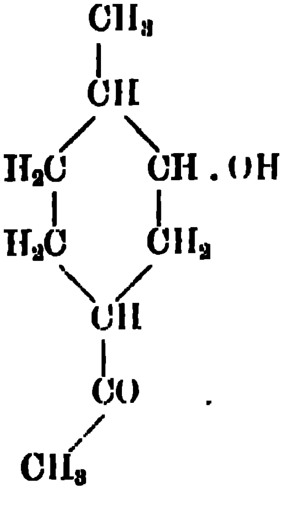


Carvone. Dihydrocarveol.

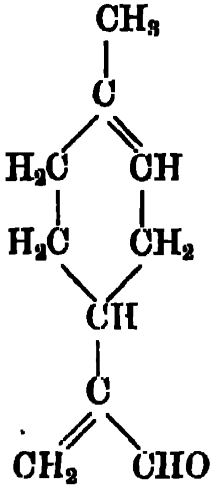
V. On oxidation, dihydrocarveol gives a trihydroxyhexahydrocymene—



VI. On further oxidation a ketone alcohol is formed-

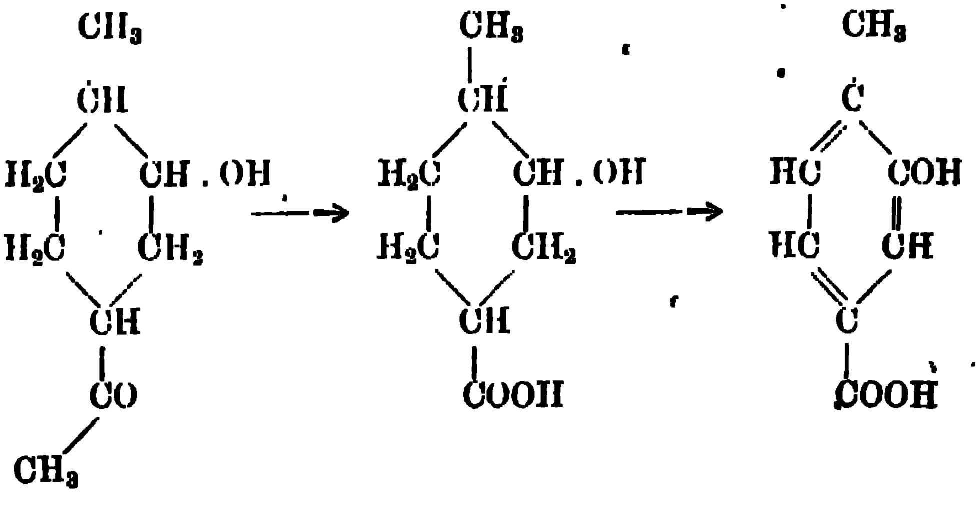


The production of this substance proves what was previously stated in I. and IV., *viz.*, that the nitrosyl chloride attacks the nucleus, and that in the reduction to dihydrocarveol the side-chain double bond is not reduced. If the nitrosyl chloride had attacked the side-chain we should, at Stage III., have formed an aldehyde of the type—



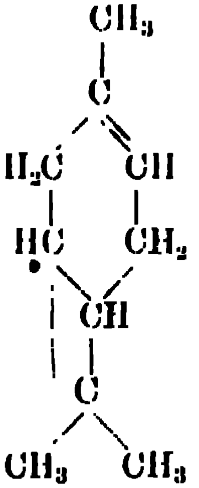
instead of the ketone produced in practice. If the side-chain had been reduced in Stage IV. instead of the nucleus, the nucleus would have been attacked by the oxidizing agent in Stage V., the ring would have been broken, and a ketonic *acid* would have been formed, just as in the case of the oxidation of terpineol.

VII. Further oxidation of the ketonic alcohol produced in Stage VI. yields a hydroxy-acid, which, by the action of bromine at 190° C., loses six hydrogen atoms, and is converted into hydroxy-*p*-toluic acid—

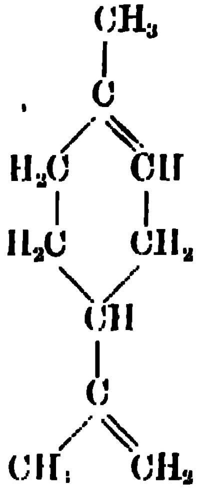


To sum up the matter, we may point out that the series of reactions IV. to VII. prove that the "isopropyl group" contains a double bond, which must also be present in dipentene. Moreover, since this double bond has persisted throughout the whole series of reactions I. to IV., it cannot have been the point at which the nitrosyl chloride attached itself, as this portion of the molecule has given rise to the —CH.OH— group. Further, the nitroso-group must have attached itself to the carbon atom to which the hydroxyl group is attached in the aromatic acid, *i.e.*, the one next that which carries the methyl group. These reactions can only be explained by assuming that dipentene has the structure which we attributed to it on account of its synthesis from terpineol.

It might be objected that we have not taken into account the possibility that, in the formation of dipentene, the elimination of water from terpineol may take place between two *non-adjacent* carbon atoms, giving rise to some such compound as—



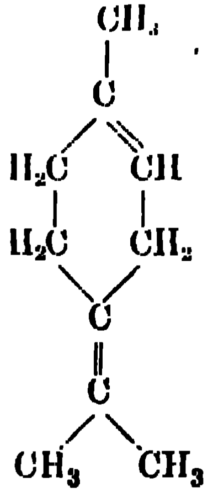
Any attempt to explain the question on these lines leads, however, to impossible results, and it may be taken as proved beyond doubt by the above experimental data that the structure of dipentene is as shown in the annexed formula. This, in turn, proves the formulæ of dextro- and lævo-limonene, for as they are the optical antipodes of which dipentene is the racemic variety, they also must possess the same structural formula as dipentene—



Dipentene.

5. *The Constitutions of Terpinolene and Terpinene.*

In the last section it was pointed out that the dehydration of terpineol might follow either of two courses: the one leading to a compound containing an asymmetric carbon atom, the other to a symmetrical derivative. The result of dehydration by means of acid potassium sulphate was shown to be dipentene; but when terpineol is dehydrated[1] by means of alcoholic sulphuric acid, an isomeric compound is formed which has the second of the two possible formulæ. This substance is terpinolene—



When terpinolene is treated with acids, it is converted into a substance which was originally assumed to be a single hydrocarbon, terpinene; and for a considerable time the constitution of terpinene was one of the riddles of organic chemistry. From the results of his investigations, Wallach[1] deduces that there is no such thing as a pure "terpinene"; but that the material to which this name has been given is a mixture of three different chemical individuals for which he proposes the following names and formulæ:—[1]

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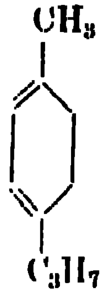
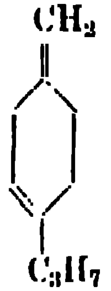
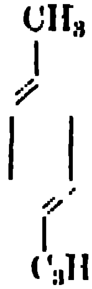
[1] Wallach, *Ber.*, 1879, **12**, 1022.

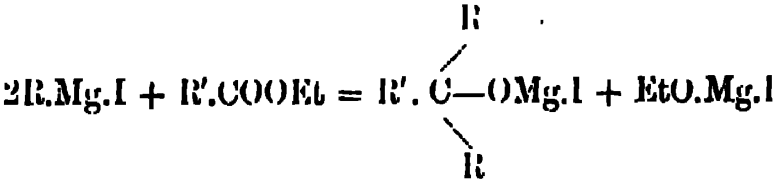

α-Terpinene.


β-Terpinene.

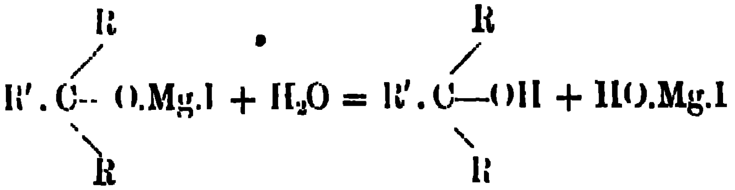

γ-Terpinene.

6. *Terpin and Cineol.*

Grignard[2] and others have shown that when the esters of organic acids react with organo-magnesium compounds, tertiary alcohols can be produced—

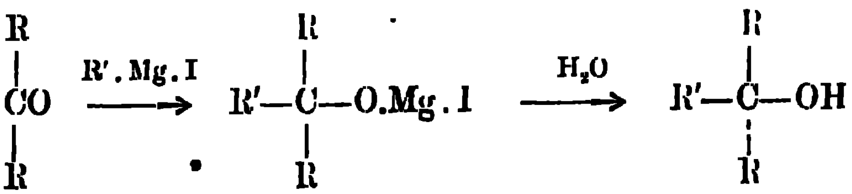


$$2R.Mg.I + R'.COOEt = R'.\overset{R}{\underset{R}{C}}—OMg.I + EtO.Mg.I$$



$$R'.\overset{R}{\underset{R}{C}}—O.Mg.I + H_2O = R'.\overset{R}{\underset{R}{C}}—OH + HO.Mg.I$$

Again, when ketones are treated with Grignard's reagent,[3] tertiary alcohols are formed—



$$\overset{R}{\underset{R}{CO}} \xrightarrow{R'.Mg.I} R'—\overset{R}{\underset{R}{C}}—O.Mg.I \xrightarrow{H_2O} R'—\overset{R}{\underset{R}{C}}—OH$$

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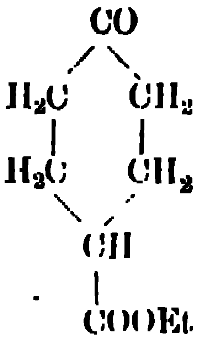
[1] Wallach, *Annalen*, 1910, 374, 224; 1906, 350, 142; *Terpene und Campher*, 1906, pp. 467-81.

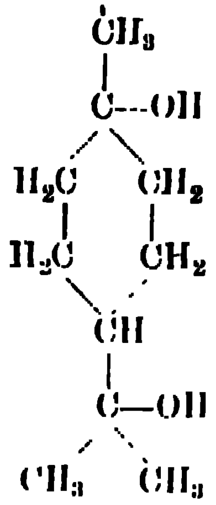
[2] Grignard, *C.R.*, 1901, 132, 336.

[3] Zelinsky, *Ber.*, 1901, 36, 3950.

Kay and Perkin[1] have combined these two reactions into one by using a ketonic ester and allowing both vulnerable groups to be attacked simultaneously. By this means, from cyclo-hexanone-4-carboxylic ester, they obtained the dihydric alcohol, terpin—



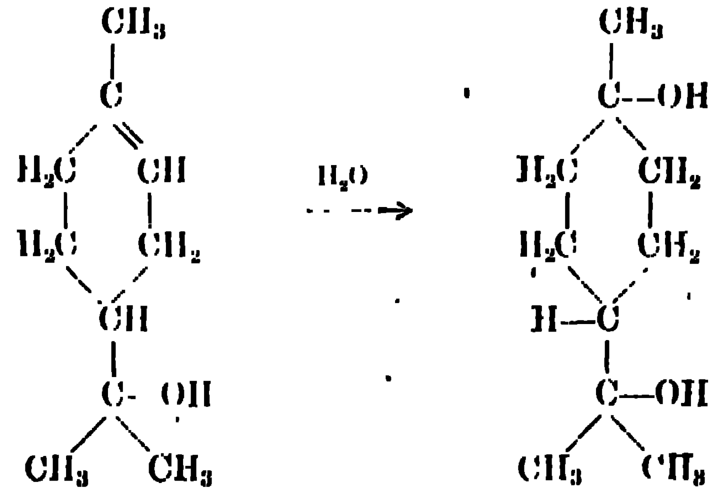
Cyclohexanone-4-carboxylic ester



Terpin.

This synthesis proves the formula of terpin beyond any dispute.

Terpin may be also obtained by boiling terpineol with dilute sulphuric acid—



Terpineol. Cis-terpin.

The terpin which is obtained in either of these ways is called *cis*-terpin, from the fact that in its space formula the two hydroxyl groups lie on the same side of the hexamethylene ring, while in the isomeric compound, *trans*-terpin, they lie on opposite sides of the ring—

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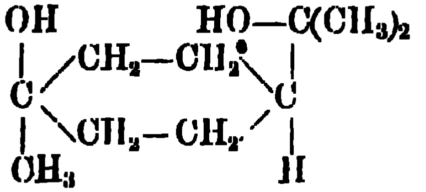
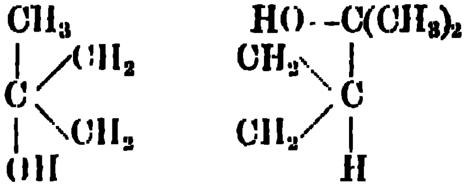
[1] Kay and Perkin, *Trans. Chem. Soc.*, 1907, 91, 372.



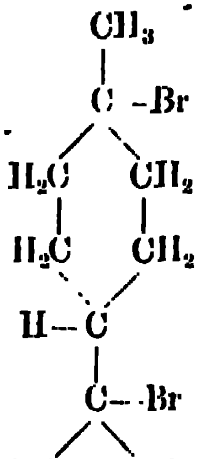
Cis-terpin.



Trans-terpin.

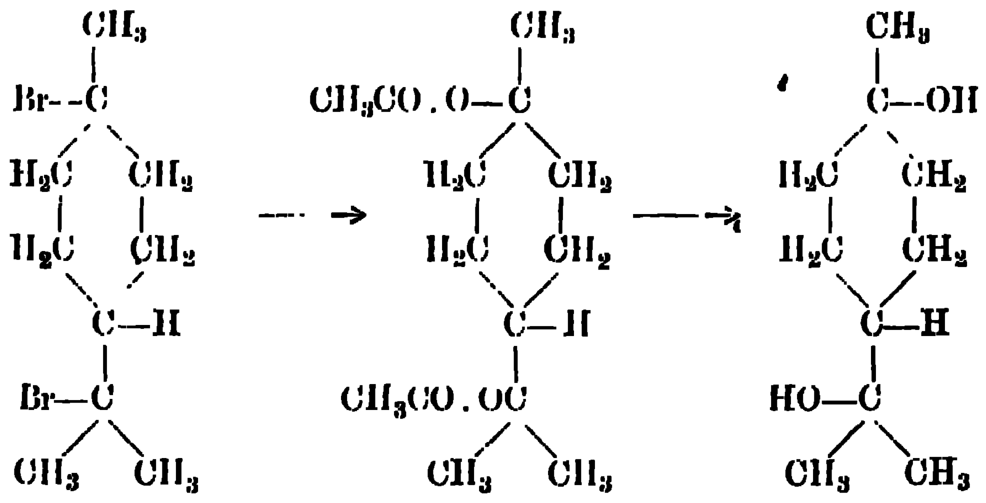
Cis-terpin unites with one molecule of water to form terpin hydrate, a crystalline substance from which it can be regenerated at 100° C. The trans-isomer does not unite with water at all.

Cis-terpin cannot be directly converted into trans-terpin, but the change can be effected by a somewhat roundabout method. In the first place, cis-terpin is subjected to the action of hydrobromic acid, by which means a dibromide is formed. As can be seen from its formula, this substance is identical with the hydrobromide of dipentene—



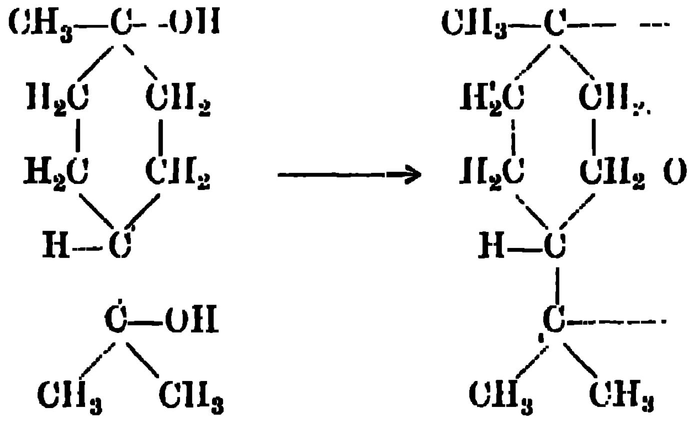
Dipentene dihydrobromide
(Cis-terpin dibromide).

This dibromide is next treated with silver acetate in acetic acid solution, and the diacetate so produced is hydrolyzed with alcoholic potash, yielding *trans*-terpin—



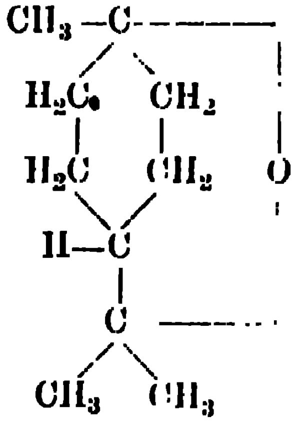
It should be noted that when cis-terpin is converted into its dibromide the product is the *cis*-form of dipentene dihydrobromide; while, on the other hand, the action of hydrobromic acid on trans-terpin produces the *trans*-variety of dipentene dihydrobromide. Thus the change of cis-terpin into trans-terpin cannot be carried out through the bromides alone, as during their formation no change from cis- to trans-form takes place; this only occurs during the hydrolysis of the acetyl derivative.

When cis-terpin is dehydrated, it yields a variety of products (terpineol, dipentene, terpinene, and terpinolene), among which is found the compound cineol, $C_{10}H_{18}O$. This substance contains neither a hydroxyl nor a carbonyl radical, and must therefore be an ether. On this view, its formation from cis-terpin is easily explained—

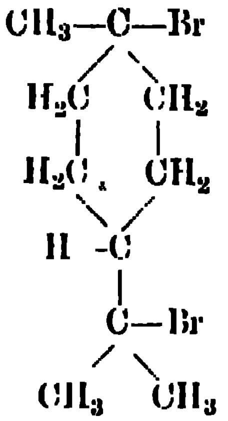


Cis-terpin. Cineol.

This formula is supported by the fact that hydrobromic acid in acetic acid solution converts cineol into cis-dipentene dibromide—

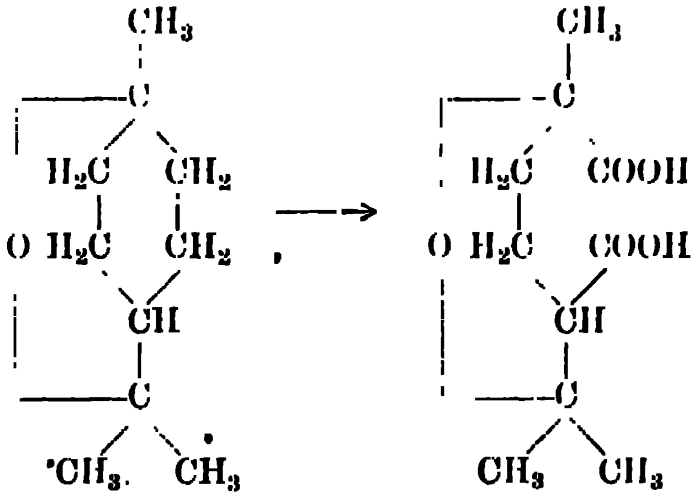


Cineol.



Cis-terpin dibromide.

The behaviour of cineol on oxidation with potassium permanganate is curious.[1] The first effect is to break the hexamethylene ring, while leaving the ether chain untouched; in this way cineolic acid is produced—



Cineol. Cineolic acid.

When cineolic acid is treated with acetic anhydride it yields cineolic anhydride, which, on dry distillation, breaks down quantitatively into carbon monoxide, carbon dioxide, and methyl-heptenone, an aliphatic ketone of considerable interest from its relations to the terpenes—

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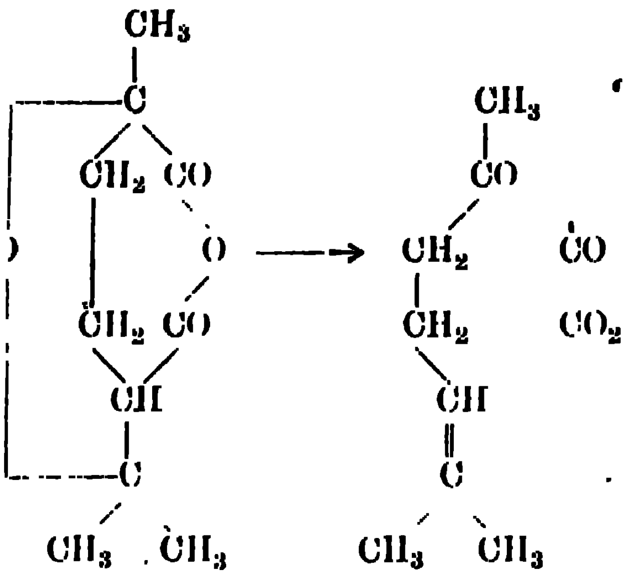
[1] Wallach and Gildemeister, *Annalen*, 1888, 246, 268; Wallach, *ibid.*, 1890, 258, 319; Wallach and Elkeles, *ibid.*, 1892, 271, 21.



Cineolic anhydride. Methyl-heptenone.

7. *The Synthesis of Carvestrene.*

Until recently, carvestrene could be obtained only by a very long and complicated series of reactions; and the constitutions of some of the intermediate compounds produced had not been well established. Perkin and Tattersall[1] have now succeeded in synthesizing it by a series of reactions analogous to those employed by Perkin in his synthesis of terpineol.

The starting-point of this new synthesis was *m*-hydroxybenzoic acid. This was first reduced with sodium and alcohol, forming hexahydro-*m*-hydroxy-benzoic acid; from which, by oxidation with chromic acid, γ-keto-hexahydrobenzoic acid (I.) was obtained. The ester of this acid reacts with magnesium methyl iodide, giving the lactone of γ-hydroxy-hexahydro-*m*-toluic acid (II.). When this is heated with hydrobromic acid it yields γ-bromohexahydro-*m*-toluic acid (III.), which on treatment with pyridine loses hydrobromic acid, and is changed into tetrahydro-*m*-toluic acid (IV.). After esterification, this is treated with magnesium methyl iodide and water, whereby an alcohol (V.) is produced which differs from terpineol in that the hydroxyl and methyl groups are in the 1, 3-position to each other, while in terpineol they are in the 1, 4-position. Just as terpineol, when treated with acid potassium sulphate, loses water to form dipentene, this new alcohol loses water and forms carvestrene (VI.)—

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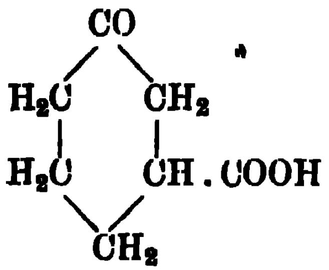
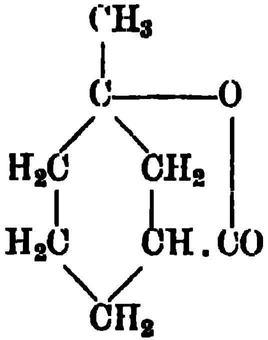
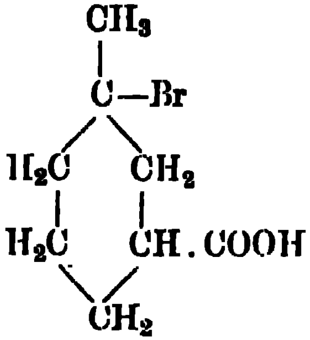
[1] Perkin and Tattersall, *Trans. Chem. Soc.*, 1907, **91**, 480.



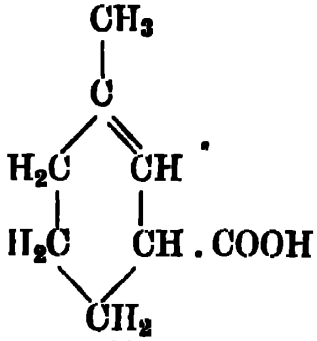
(I.)



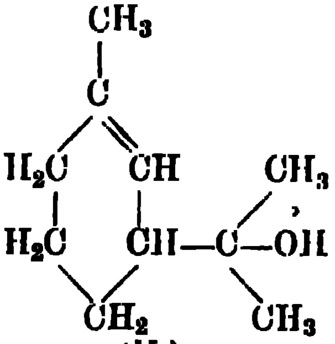
(II.)



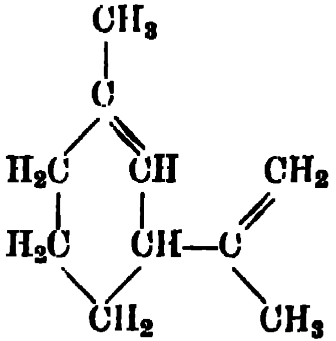
(III.)



(IV.)

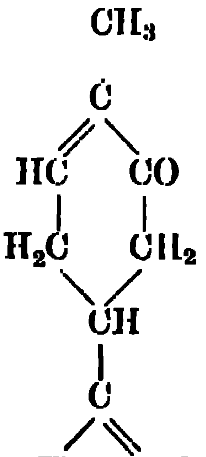


(V.)

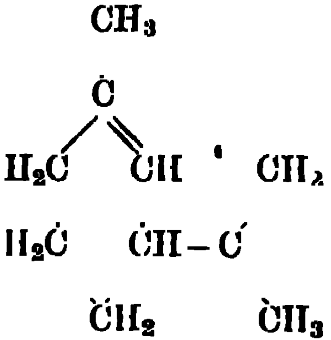


(VI.)

Though since the discovery of this new synthesis the old way of preparing carvestrene has lost its value as a practical method, we may give a very brief description of it here on account of one transition which occurs in the course of the reactions. The starting-point for the old synthesis was the substance carvone, which we have already encountered. Now, as can be seen from the formulæ of the two substances, to convert carvone into carvestrene we must shift the isopropylene group from one carbon atom to the adjacent one. How this is done will be seen in due course.

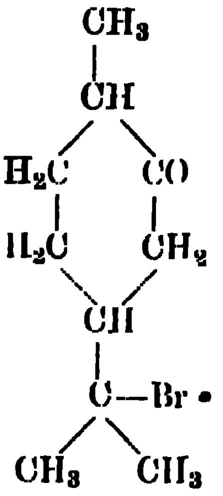


Carvone.



Carvestrone.

Carvone is first reduced with zinc dust and alcoholic potash to dihydrocarvone; hydrobromic acid is then added on, giving dihydrocarvone hydrobromide *—



Now, when this substance is treated with alcoholic potash it

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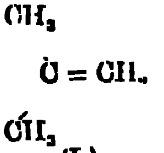
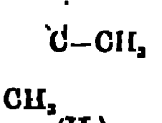
* When a halogen acid is added on to the double bond of an unsaturated substance, the negative part (*i.e.*, the halogen atom) always unites with that carbon atom to which the *fewest* hydrogen atoms are attached. For example, in the case given below the compound formed by the addition of hydrobromic acid to (I.) is (II.) and not (III.).



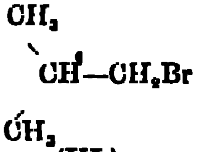
$\underset{CH_3}{\overset{CH_3}{C}} = CH_2$

(I.)



$\underset{CH_3}{\overset{CH_3\,Br}{C}}-CH_3$

(II.)

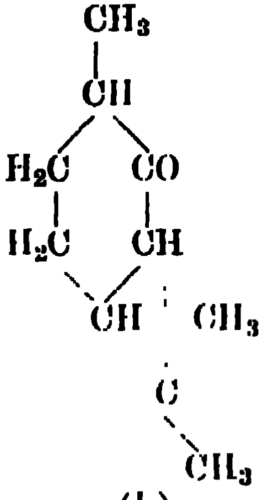


$\underset{CH_3}{\overset{CH_3}{CH}}-CH_2Br$

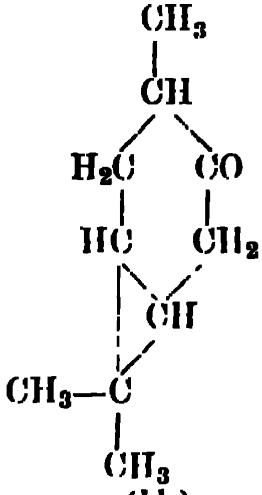
(III.)

This is called the "Markownikoff Rule" (*Ber.*, 1869, **2**, 660; *Annalen*, 1870, **153**, 256). Compare, however, Cuy, *J. Amer. Chem. Soc.*, 1920, **42**, 503.

gives up hydrobromic acid, but instead of regenerating a carvone derivative it yields a new ketone, carone. Since on oxidation carone yields 1, 1-dimethyl-2, 3-trimethylene dicarboxylic acid (caronic acid), it must contain a trimethylene ring. The simplest way in which this can be explained is to assume that carone has either of the formulæ (I.) and (II.)



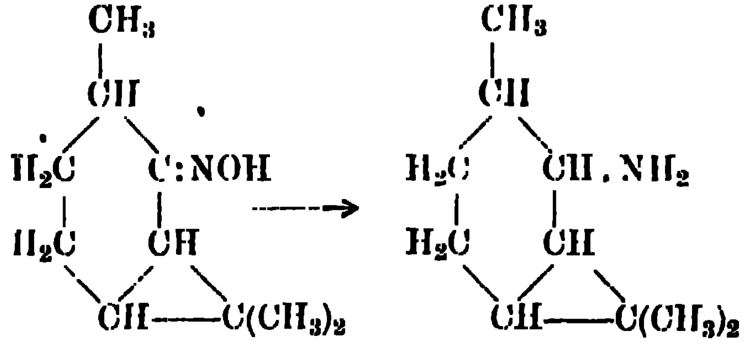
(I.)



(II.)

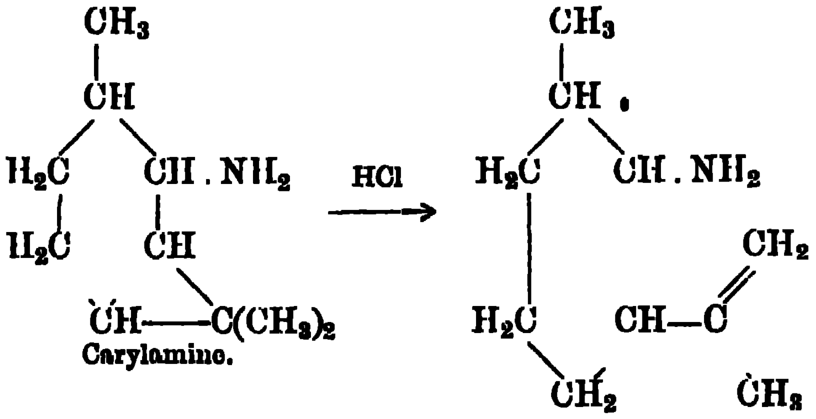
The first of these formulæ is the one usually ascribed to carone. We cannot enter into the details of the evidence here.

When carone is allowed to react with hydroxylamine it forms the substance carone oxime, which, on reduction, produces the amino-compound carylamine—



Carone oxime. Carylamine.

When this body is treated with alcoholic acid it undergoes isomeric change, and is converted into the hydrochloride of vestrylamine, the trimethylene ring being now broken. By this means we have transferred the isopropylene group from one carbon atom to the other.



Carylamine.

Vestrylamine.

Vestrylamine hydrochloride, on dry distillation, breaks down into carvestrene by loss of ammonium chloride—

$$C_{10}H_{17}.NH_2.HCl = C_{10}H_{16} + NH_4Cl$$

Carvestrene is a racemic compound, the dextro-antipode of which is found in nature as sylvestrene.[1] The latter has been synthesized by Perkin.[2]

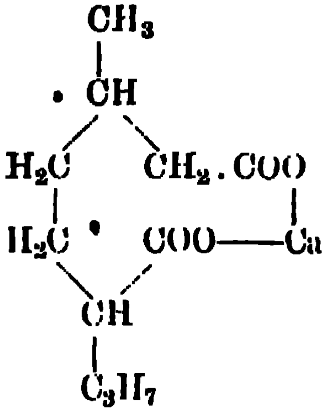
8. *The Synthesis of Menthone.*

Though menthone had been synthesized in different ways by Einhorn and Klages,[3] Kötz and Hesse[4] and Haller and Martine,[5] none of these methods furnished any proof of the constitution of the substance. It was not until 1907 that synthetic evidence was obtained upon this point.

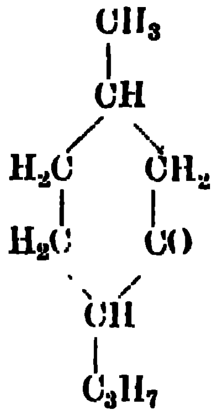
Kötz and Schwarz[6] first synthesized β-methyl-α'-isopropyl-pimelic acid, and by the distillation of its calcium salt they produced menthone—

---

[1] Baeyer, *Ber.*, 1894, **27**, 3485.
[2] Perkin, *Proc.*, 1910, **6**, 97.
[3] Einhorn and Klages, *Ber.*, 1901, **34**, 3793.
[4] Kötz and Hesse, *Annalen*, 1905, **342**, 306.
[5] Haller and Martine, *C.R.*, 1905, **140**, 130.
[6] Kötz and Schwarz *Annalen*, 1907, **357**, 206.

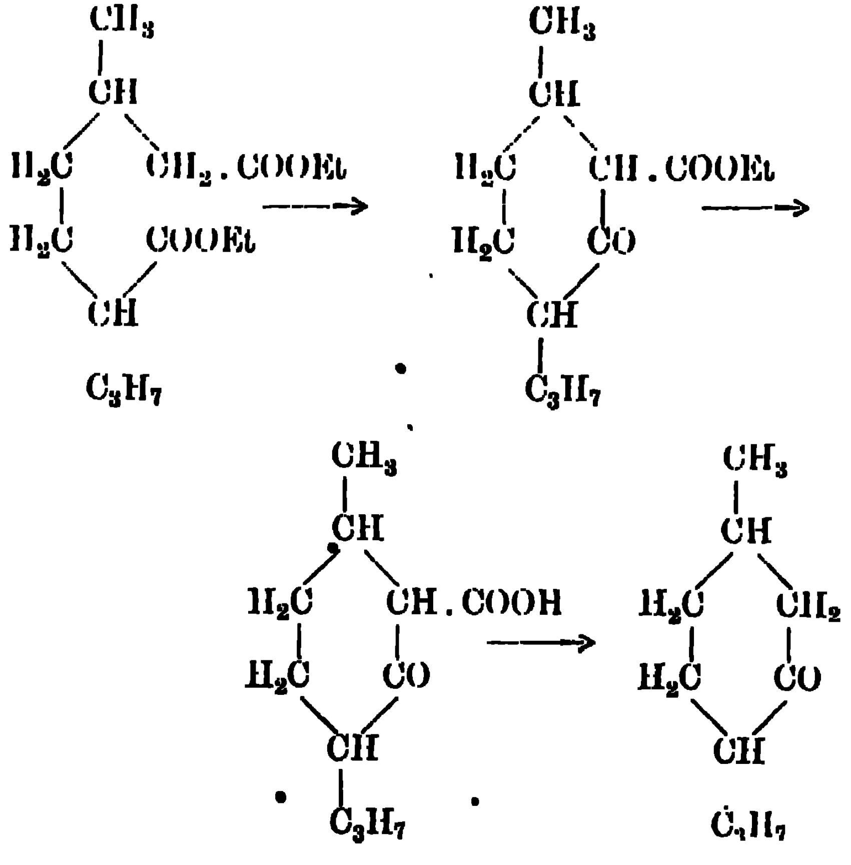


Calcium β-Methyl-α′-isopropyl-pimelate.



Menthone.

A similar result is obtained by making the ester of this acid undergo intramolecular acetoacetic ester condensation by means of sodium, and then hydrolysing the ester thus obtained and splitting off carbon dioxide in the usual way—

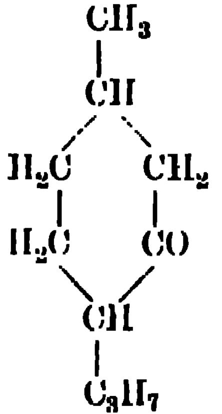


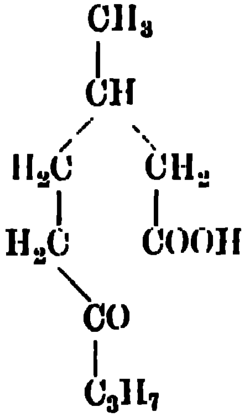
By means of this synthetic method, Kötz and Schwarz have produced an active menthone which is strongly dextro-rotatory.

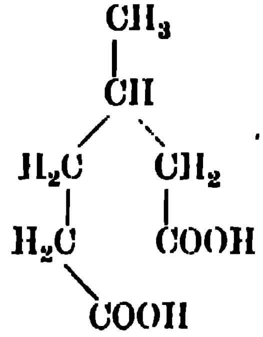
9. *The Decompositions of Menthone.*

Before the discovery of the syntheses which we have just described, it had not been possible to show synthetically that the methyl and isopropyl radicles in menthone lay in the para-position to each other. The evidence for this had, however, been obtained from the decomposition reactions of menthone.

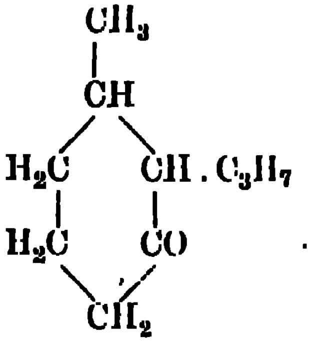
When menthone is oxidized by means of potassium permanganate, the first product is hydroxymenthylic acid,[1] which, on further oxidation, is converted into β-methyl-adipic acid—

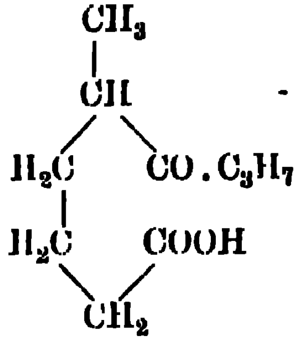

Menthone.

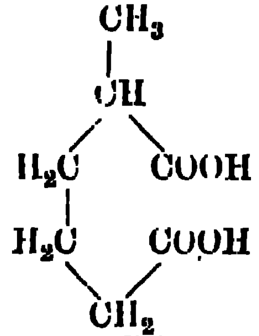

Hydroxymenthylic acid.


β-Methyl-adipic acid.

These substances could be formed only if the isopropyl and methyl radicles were in the para-position to each other; for if we take them in any other position, as shown below, the resulting products are not the same—




Keto-acid.


α-Methyl-adipic acid.

Again, the action of phosphorus pentachloride on menthone gives a dichloro-tetrahydro-cymene,[1] which, by successive treatment with bromine and quinoline, produces a chlorocymene[2] of the constitution—

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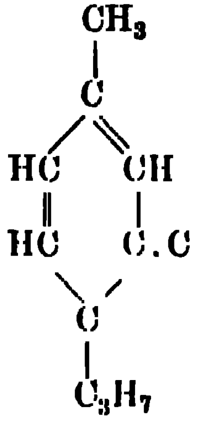
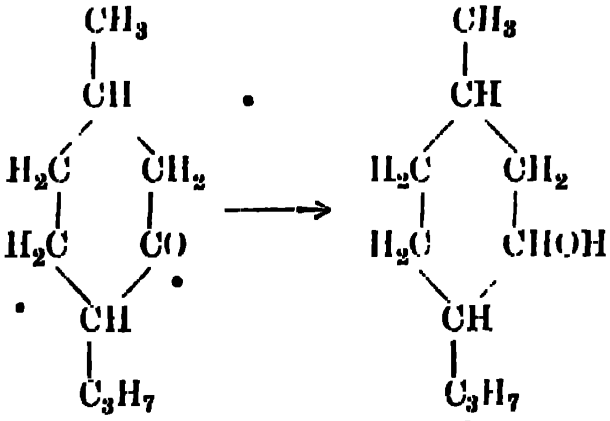
[1] Arth, *Ann. Chim. Phys.*, 1886, VI., 7, 433; Beckmann and Mehrländer, *Annalen*, 1896, **289**, 367.



10. *The Synthesis and Constitutions of Menthol and Menthene.*

Menthol is the alcohol corresponding to menthone, from which it can be prepared by reduction. Since we have established that menthone is (I.) it is obvious that menthol must be (II.)—



(I.) (II.)

Now, when we dehydrate menthol, a hydrocarbon, *d*-menthene, is formed. This might be either (A) or (B), since we can suppose that water is removed in either of two ways—

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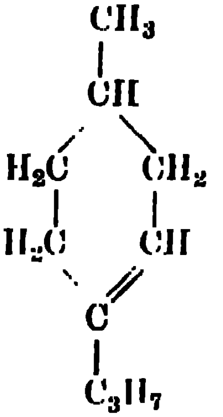
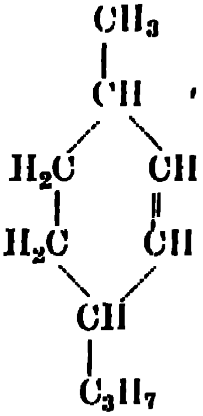
[1] Berkenheim, *Ber.*, 1892, **25**, 694.

[2] Jünger and Klages, *Ber.*, 1896, **29**, 314.

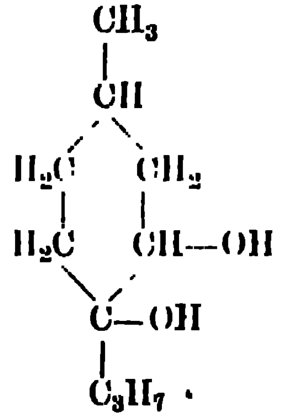


(A.)

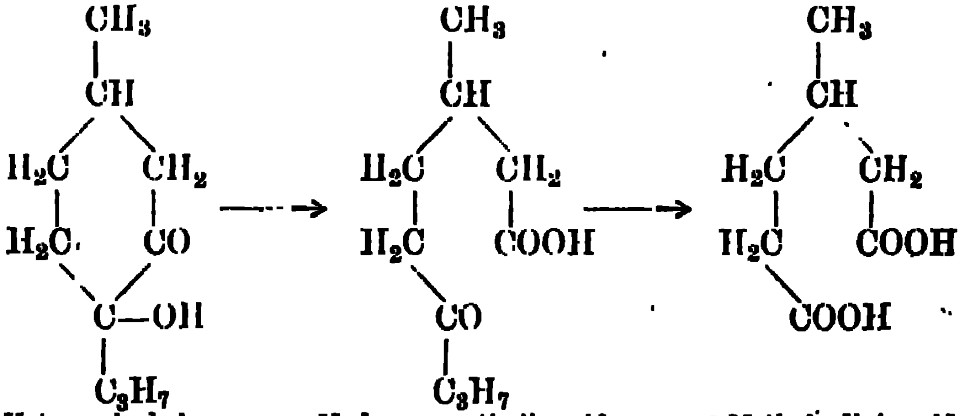


(B.)

The decision between the two formulæ can be made by the aid of the evidence of the oxidation products of menthene.[1] When the menthene obtained from menthol is oxidized with potassium permanganate solution, the first product is a glycol, which, according to formula (A), would have the constitution—



Further oxidation yields a ketone-alcohol, then hydroxymenthylic acid, and finally β-methyl-adipic acid—

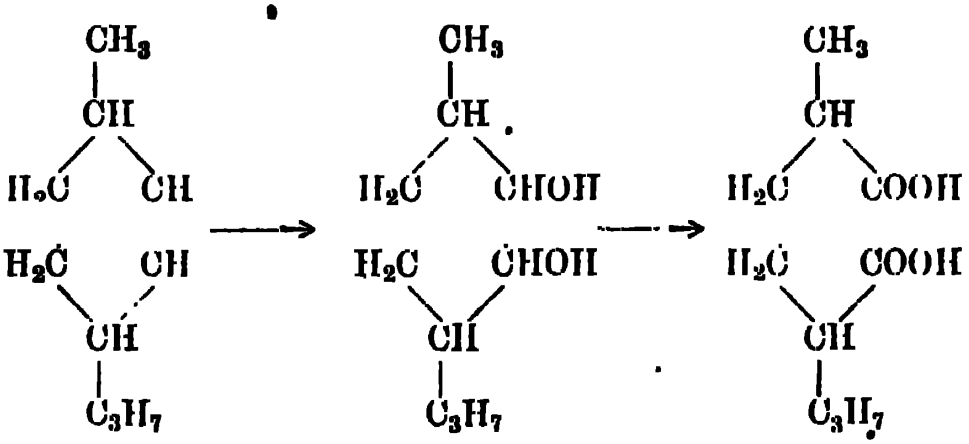


Ketone alcohol. Hydroxymenthylic acid. β-Methyl-adipic acid.

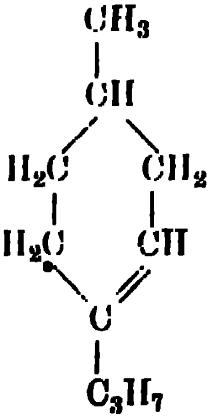
---

[1] Wagner, *Ber.*, 1894, 27, 1639.

This is in agreement with the experimental results; but if, on the other hand, we start from the second possible formula for menthene, the oxidation products would not be those found in practice, but would be the compounds shown below—

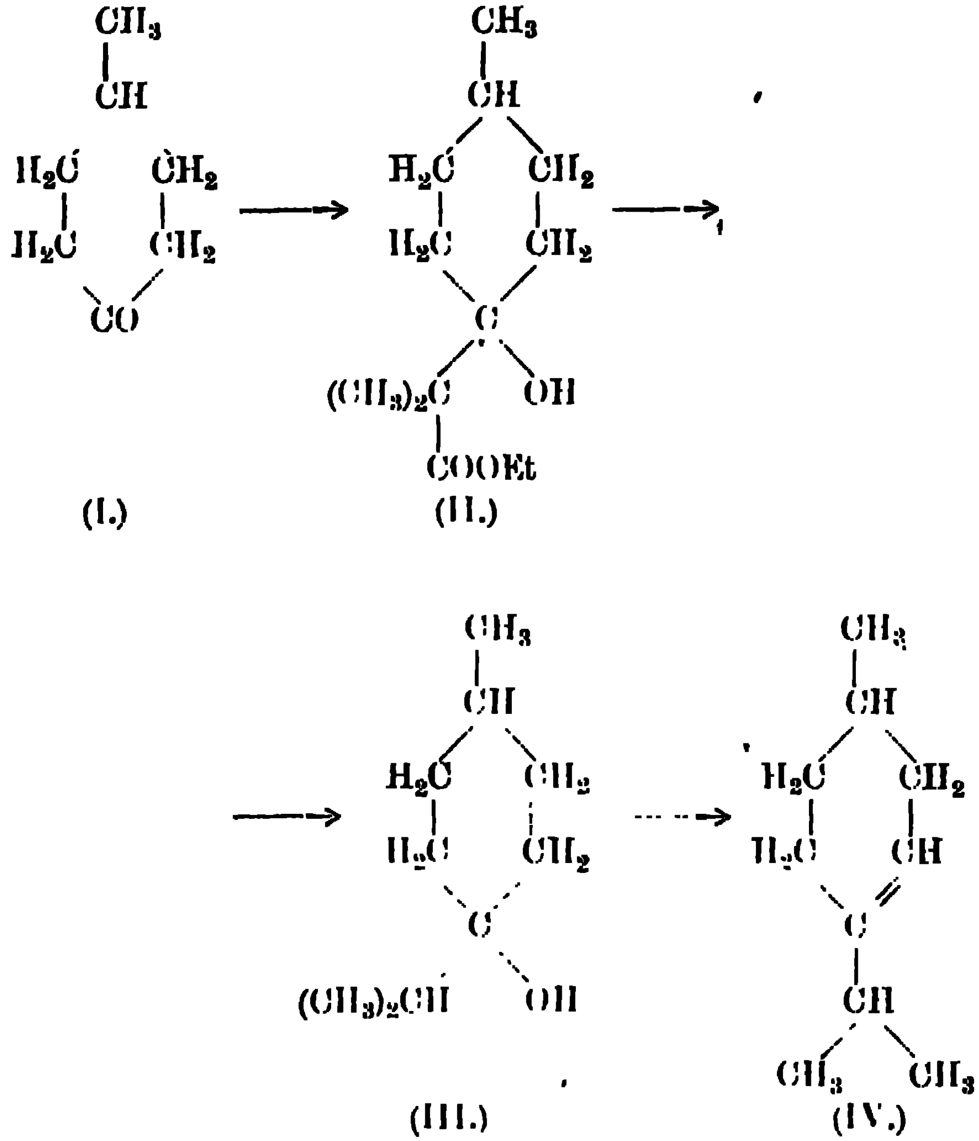


Thus the constitution of menthone must be—



This has been confirmed by Wallach's recent synthesis of menthene,[1] in which he chooses as his starting-point 1, 4-methylcyclohexanone (I.). This he condenses with α-bromo-isobutyric ester by means of zinc, forming (II.); and then, by hydrolysis and heating, causes the acid to lose carbon dioxide and become converted into an alcohol (III.), which, on boiling with sulphuric acid, loses water and yields menthene—

[1] Wallach, *Ber.*, 1906, **39**, 2504.



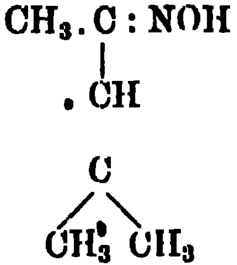
(I.) (II.) (III.) (IV.)

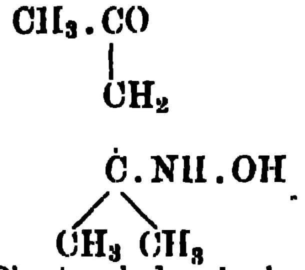
Menthone.

11. *The Constitution of Pulegone.*

The last compound of the menthone group with which we need deal is the unsaturated ketone pulegone.

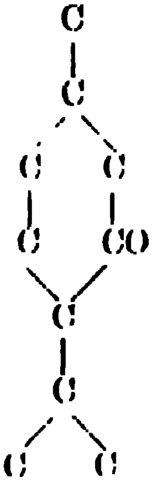
If a ketone contains a double bond in the $\alpha\beta$-position to the carbonyl group, hydroxylamine may react with it in two ways: forming an oxime in the one case, and in the other attaching itself to the double bond to give a hydroxylamine derivative. For instance, in the case of mesityl oxide, we may have either mesityl oxime or diacetone-hydroxylamine produced—


Mesityl oxime.

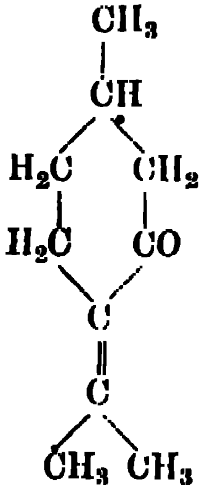

Diacetone-hydroxylamine

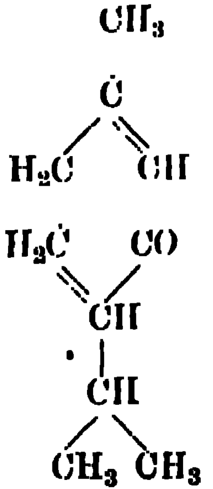
Now, since pulegone shows a similar behaviour, forming either an oxime or a hydroxylamine derivative, the presumption is that it also is a ketone with an unsaturated group in the $\alpha\beta$-position to the carbonyl radical.

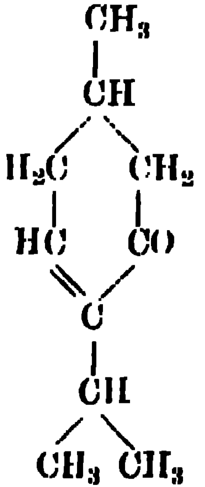
Again, pulegone on reduction is converted into menthone, so that it must contain the skeleton—



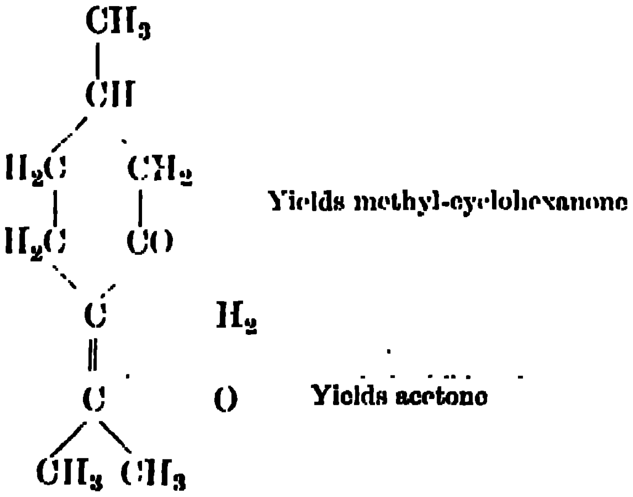
And since we have found that it has the properties of an $\alpha\beta$ unsaturated ketone it can have only three possible formulæ—


(A.)


(B.)


(C.)

The evidence which enables us to choose between these three has been supplied by Wallach,[1] who has shown that when pulegone is heated under pressure with water or anhydrous formic acid it undergoes decomposition into acetone and methyl-cyclohexanone. Since this reaction can be explained by Formula A alone, it is obvious that pulegone must have that constitution. The break-down may be formulated in the way indicated below—



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[1] Wallach, *Annalen.*, 1896, **289**, 337.

CHAPTER III

THE DICYCLIC TERPENES

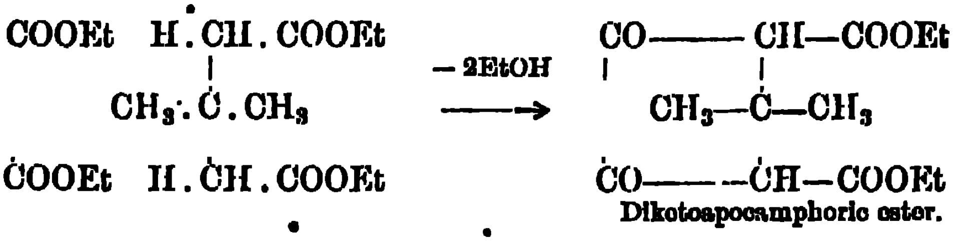
A.—THE CAMPHENE-BORNYLENE GROUP

1. *Syntheses of Camphoric Acid.*

IN the series of dicyclic terpenes which we are about to describe there are three important classes of substances. One group is derived from the hydrocarbon camphene, another from fenchone, and a third from pinene. Of these by far the most important is the camphene group, with which we shall deal first. The central substance of this group is the compound camphor, $C_{10}H_{16}O$; but in order to prove the constitution of this body it will be necessary to proceed step by step, and in the first place to prove the constitution of camphoric acid, which is obtained from camphor by oxidation.

Komppa[1] and, later, Perkin and Thorpe[2] have synthesized camphoric acid. We may deal with both of these syntheses, beginning with the method employed by Komppa.

In this synthesis, the starting materials are oxalic ester and ββ-dimethyl-glutaric ester. These are condensed together with sodium ethylate in the usual way, producing diketoapocamphoric ester—



$$\begin{array}{lcl} \begin{array}{ll} COOEt & H.CH.COOEt \\ & \quad | \\ & CH_3.C.CH_3 \\ & \quad | \\ COOEt & H.CH.COOEt \end{array} & \xrightarrow{-2EtOH} & \begin{array}{l} CO——CH—COOEt \\ | \qquad\qquad | \\ | \quad CH_3—C—CH_3 \\ | \qquad\qquad | \\ CO——CH—COOEt \end{array} \end{array}$$

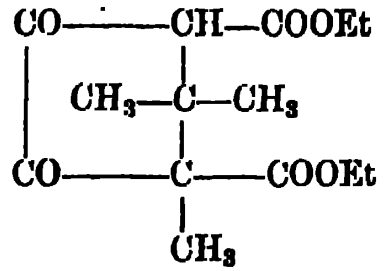
Diketoapocamphoric ester.

This was then methylated by means of sodium and methyl iodide, giving diketocamphoric ester—

---

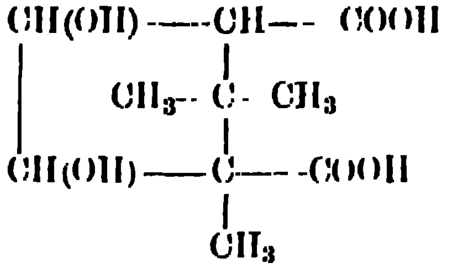
[1] Komppa, *Ber.*, 1903, **36**, 4332; *Annalen*, 1909, **368**, 126; **370**, 209.

[2] Perkin and Thorpe, *Trans. Chem. Soc.*, 1906, **89**, 795.



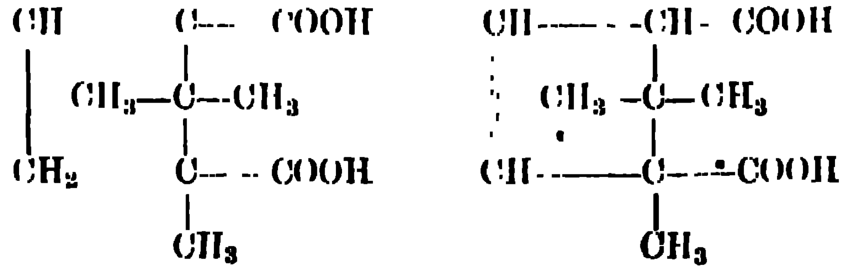
It is obvious that, since the formula is symmetrical, it makes no difference which hydrogen atom is replaced by the methyl group; the end-product in each case is the same.

This diketo-ester was dissolved in sodium carbonate solution and then treated with sodium amalgam in a stream of carbon dioxide; by this means the two carbonyl groups were reduced, and dihydroxycamphoric acid was formed, the ester being hydrolysed by the alkaline solution—



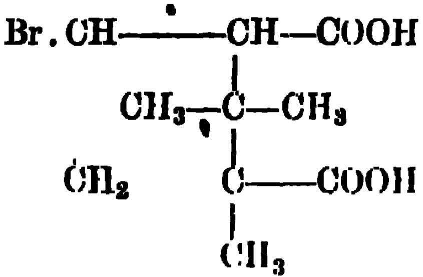
Dihydroxycamphoric acid

On boiling this substance with hydriodic acid in presence of red phosphorus, it is converted into dehydrocamphoric acid, which may have either of the constitutions shown below·

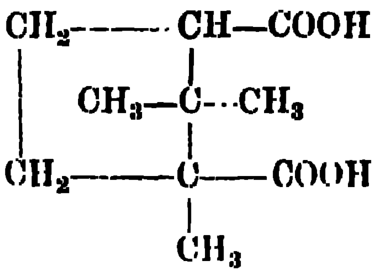


Dehydrocamphoric acid.

The constitution of this acid is of no importance, however, as the next two steps in the synthesis will yield the same final product from either of the two acids formulated above. The dehydrocamphoric acid is heated with hydrobromic acid in acetic acid solution to 125° C., whereby it is converted into a bromo-acid, which is then reduced with zinc dust and acetic acid to a substance which is identical with ordinary racemic camphoric acid—



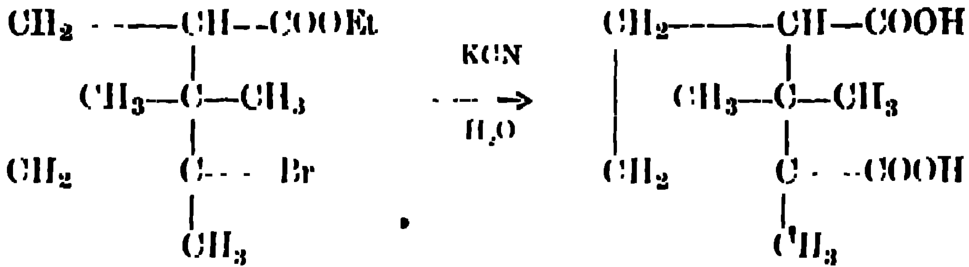
Bromo-acid.



Racemic camphoric acid.

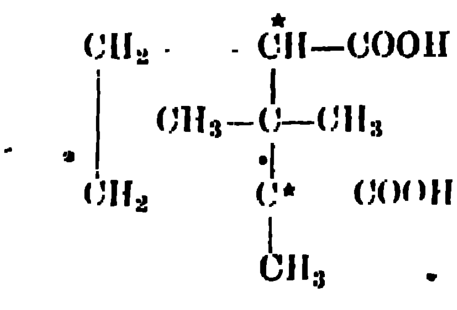
It will be seen at once that the exact constitution of the dehydrocamphoric acid is of no great importance, as the position of the bromine atom in the bromo-acid does not affect the constitution of the final camphoric acid.

The synthesis of Perkin and Thorpe starts from trimethyl-1, 2, 2-bromo-1-cyclopentane carboxylic ester, which is shaken with a mixture of potassium cyanide and hydrocyanic acid solutions. The resulting substance is heated and then boiled with acetic anhydride, whereby racemic camphoric anhydride is formed.

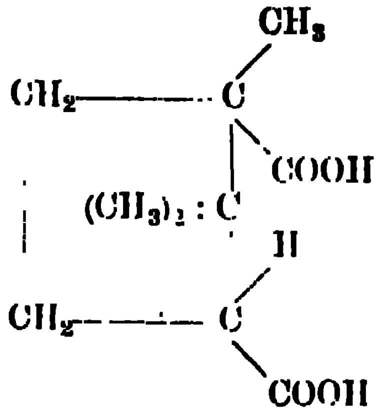


Trimethyl-bromo-cyclopentane carboxylic ester. Camphoric acid.

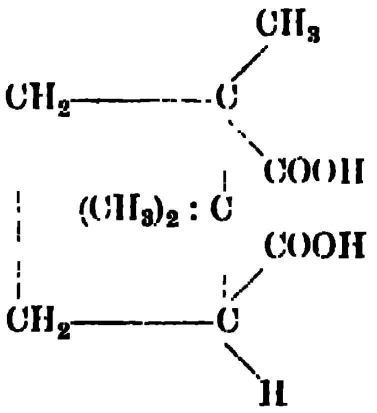
One peculiarity of camphoric acid may be pointed out here. An examination of the formula shows that camphoric acid has two asymmetric carbon atoms in its ring—these are distinguished by asterisks in the following formula:—



Now, when we attempt to racemize dextro-camphoric acid by any of the usual methods, it is found that instead of producing an equimolecular mixture of dextro- and lævo-camphoric acids we obtain merely a mixture of dextro-camphoric acid with a new substance, lævo-*iso*-camphoric acid. From this behaviour of camphoric acid it is deduced that instead of both asymmetric carbon atoms in the dextro-acid being inverted (which would give us the mirror-image lævo-camphoric) only one is altered; so that half the molecule remains as it was. The change from *d*-camphoric to *l-iso*camphoric would be represented thus—



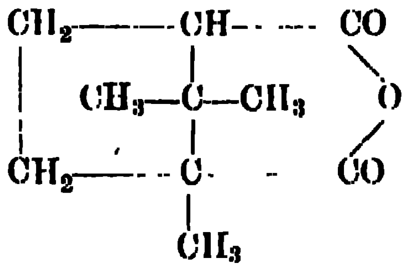
d Camphoric acid.



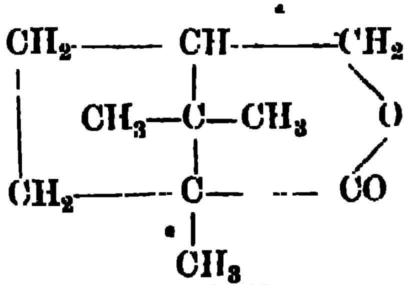
*l-Iso*camphoric acid

2. *The Synthesis of Camphor.*

From synthetic camphoric acid we can obtain camphor itself by the following method. When camphoric anhydride is treated with sodium amalgam it is reduced to campholide,[1] the reaction being analogous to the production of phthalide from phthalic acid—



Camphoric anhydride.



Campholide.

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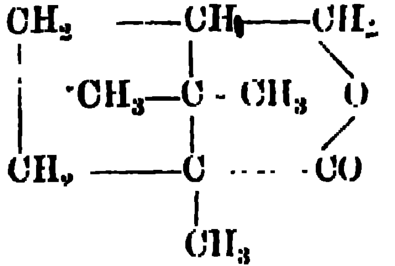
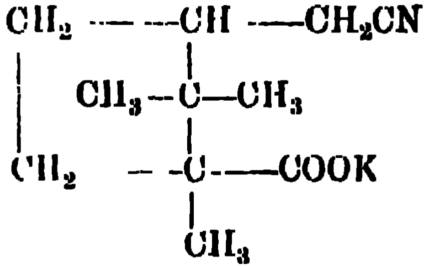
[1] Haller, *Bull. soc. chim.*, 1896, [iii.], 15, 7, 984; Forster, *Trans. Chem. Soc.*, 1896, 69, 36.

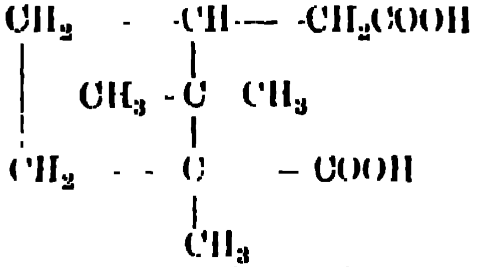
Campholide, on treatment with potassium cyanide, produces a nitrile-salt, which, on hydrolysis, gives homocamphoric acid;[1] this action is exactly like that which produces homophthalic acid from phthalide—



Campholide.

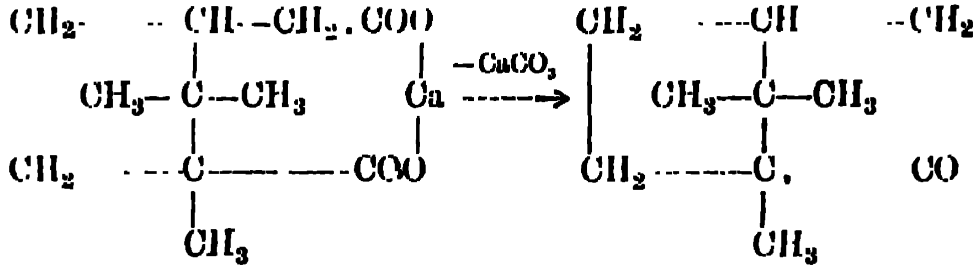


Nitrile-salt.



Homocamphoric acid.

From this homocamphoric acid it is easy to produce camphor[2] itself by distilling the lead or calcium salt of the acid—



This synthesis confirms the camphor formula which was put forward in 1893 by Bredt.[3]

3. *Borneol and Camphane.*

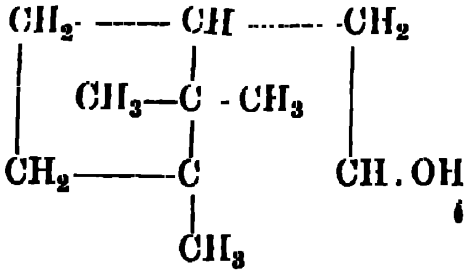
When camphor is reduced by means of sodium and alcohol[4] it yields a secondary alcohol, borneol, which has the formula—

[1] Haller and Blanc, *Compt. rend.*, 1900, 130, 376.

[2] Haller, *Compt. rend.*, 1896, 122, 446; Bredt and Rosenberg, *Annalen*, 1896, 289.

[3] Bredt, *Ber.*, 1893, 26, 3047.

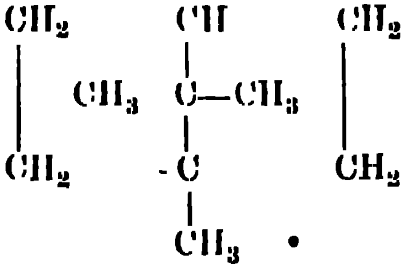
[4] Jackson and Menke, *Am. Chem. J.*, 1883, 5, 270; Wallach, *Annalen* 1885, 230, 225.



Borneol.

This alcohol occurs in dextro- and lævo-forms, either of which may be obtained at will by reducing the corresponding dextro- or lævo-camphor. Borneol is not the only product of this reaction, however, as at the same time a small quantity of an isomeric isoborneol[1] is produced, whose constitution is not yet definitely proved.

The hydroxyl radicle in borneol can be replaced by a halogen atom in the usual way,* and if the bornyl iodide thus formed be reduced by means of zinc dust, acetic and hydriodic acids,[2] a hydrocarbon camphane is produced, which is the root-substance of the camphor series. It has the formula—



Camphane.

4. *Bornylene.*

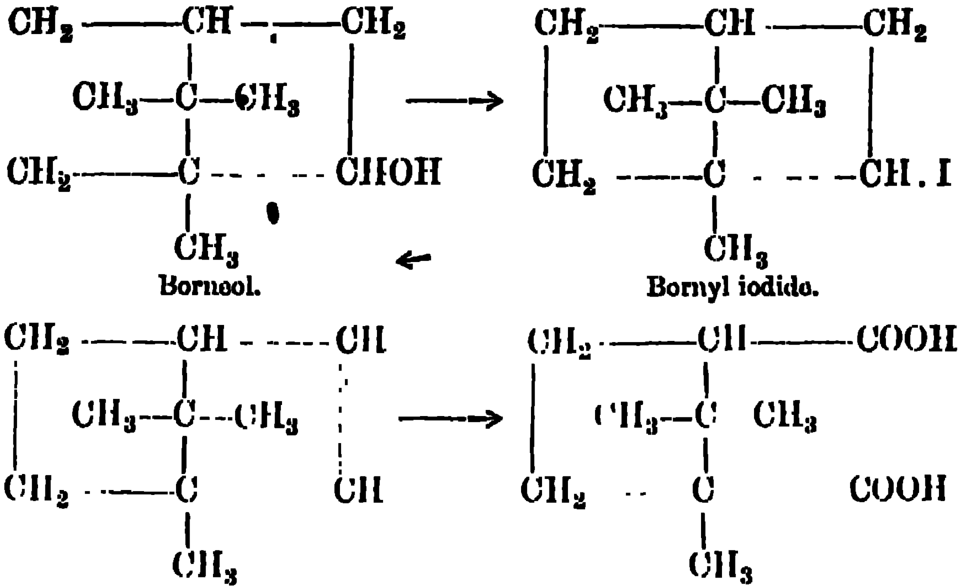
When bornyl iodide is heated with alcoholic potash to 170° it is converted into an unsaturated substance by the loss of a molecule of a halogen acid.[3] This compound, bornylene, on oxidation yields camphoric acid.

[1] Montgolfier, *Compt. rend.*, 1879, 89, 101; Haller, *ibid.*, 1887, 105, 227.

* In practice, however, bornyl iodide is usually prepared by the action of hydriodic acid on pinene, as the yields from borneol are very poor.

[2] Aschan, *Ber.*, 1900, 33, 1006.

[3] Wagner and Brickner, *Ber.*, 1900, 33, 2121.


Borneol.

Bornyl iodide.

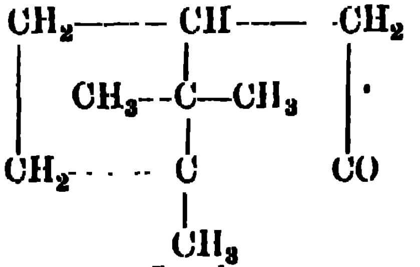
Bornylene.

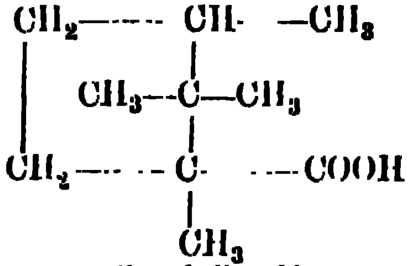
Camphoric acid.

Bornylene therefore has the structure shown above.

5. *The Decomposition Products of Camphor.*

Let us now return to the problem of camphor. The most vulnerable point in the camphor molecule is the carbonyl group and the adjacent methylene radicle. The ring at this point is so easily attacked that it may be broken by a simple hydrolytic reaction. When camphor is heated with sodium and xylene to a temperature of 280° C., the ring opens; and when the reaction mixture is poured into water, the sodium salt of campholic acid [1] is formed--


Camphor.


Campholic acid.

The same acid has been obtained by Haller and Blanc [2] from campholide, a method of synthesis which establishes the constitution of the substance beyond doubt—

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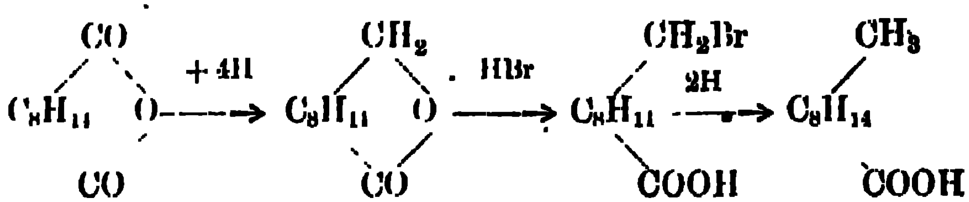
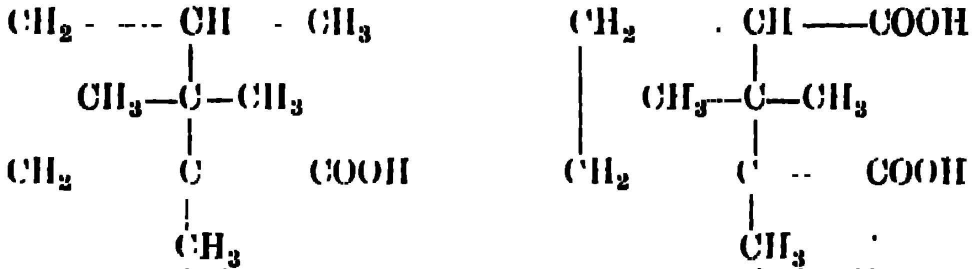
[1] Malin, *Annalen*, 1868, 145, 201; Kachler, *ibid.*, 1872, 162, 259.

[2] Haller and Blanc, *Compt. rend.*, 1900, 130, 376.



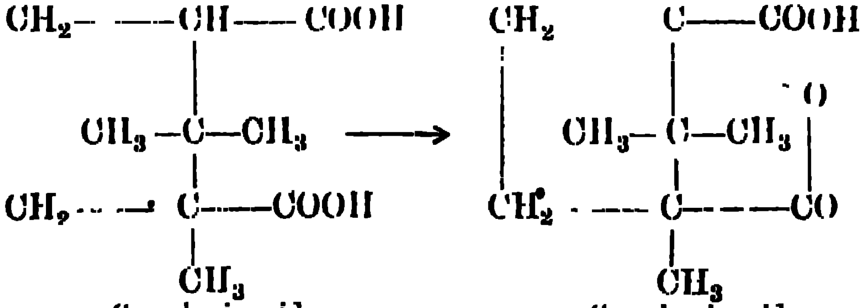
Camphoric anhydride. Campholide. Bromocampholic acid. Campholic acid.

Now, when campholic acid is oxidized with nitric acid, the newly formed methyl group is oxidized to carboxyl, and camphoric acid is formed—

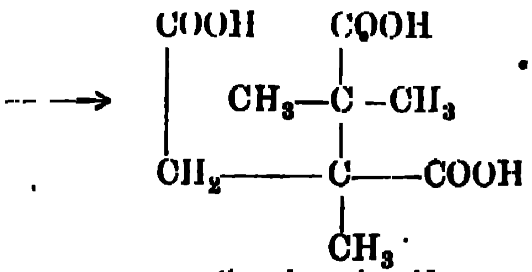


Campholic acid. Camphoric acid.

Further action of nitric acid upon the latter substance gives rise to camphanic acid, which is oxidized in its turn to camphoronic acid—



Camphoric acid. Camphanic acid.

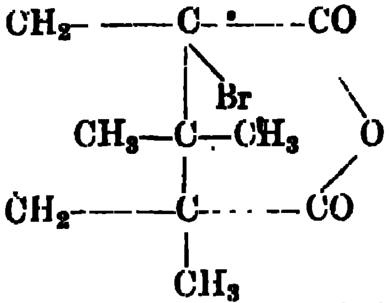


Camphoronic acid.

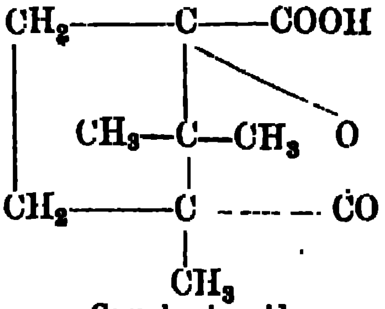
The constitution of camphanic acid[1] is proved by the fact that it can be obtained from bromocamphoric anhydride by boiling with water—

---

[1] Reyher, "Dissertation," Leipzig, 1891; Bredt, *Ber.*, 1894, 21, 2097; Lapworth and Lenton, *Trans. Chem. Soc.*, 1902, 81, 17.

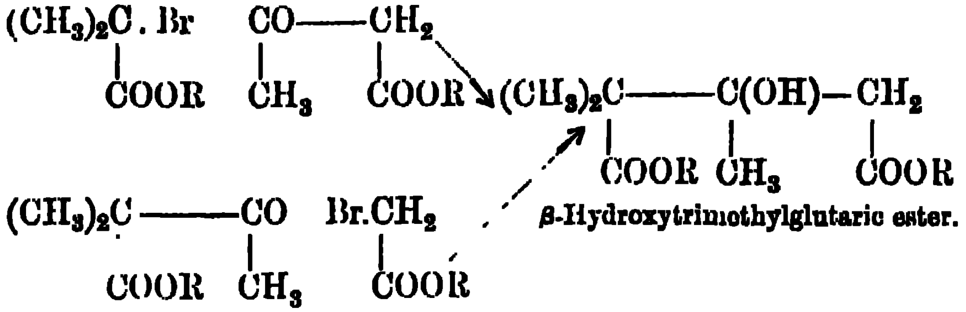


Bromocamphoric anhydride.



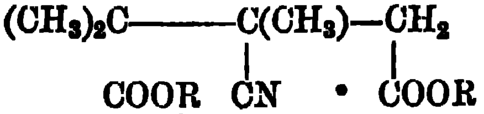
Camphanic acid.

The constitution of camphoronic acid was established by the synthesis of Perkin and Thorpe.[1] These authors first prepared β-hydroxy-trimethyl-glutaric ester by the action of zinc upon a mixture of acetoacetic ester and α-bromo-isobutyric ester, or upon a mixture of dimethyl-acetoacetic ester and monobromacetic ester—



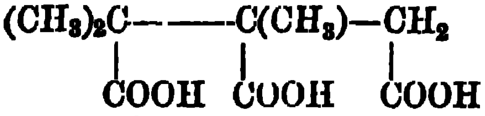
β-Hydroxytrimethylglutaric ester.

By replacing the hydroxyl group first with chlorine and then by cyanogen they obtained the nitrile ester of camphoronic acid, from which the acid itself was produced by hydrolysis—



$$\underset{\mathrm{COOR}}{(\mathrm{CH_3})_2\mathrm{C}}\text{———}\underset{\mathrm{CN}}{\mathrm{C}(\mathrm{CH_3})}\text{—}\underset{\mathrm{COOR}}{\mathrm{CH_2}}$$

Camphoronic nitrile.



$$\underset{\mathrm{COOH}}{(\mathrm{CH_3})_2\mathrm{C}}\text{———}\underset{\mathrm{COOH}}{\mathrm{C}(\mathrm{CH_3})}\text{—}\underset{\mathrm{COOH}}{\mathrm{CH_2}}$$

Camphoronic acid.

When camphoronic acid is heated to above 135° C., it loses water and is converted into anhydrocamphoronic acid, $C_9H_{12}O_5$. By brominating the chloride of this acid, two isomeric bromoanhydrocamphoronic chlorides are produced, one of which, when boiled with water, gives the lactone of an unstable hydroxycamphoronic acid (camphoranic acid), while the other yields stable hydroxycamphoronic acid. Camphoranic acid, when fused with potash, breaks down into oxalic and trimethylsuccinic acids.[1] These changes may be expressed thus—

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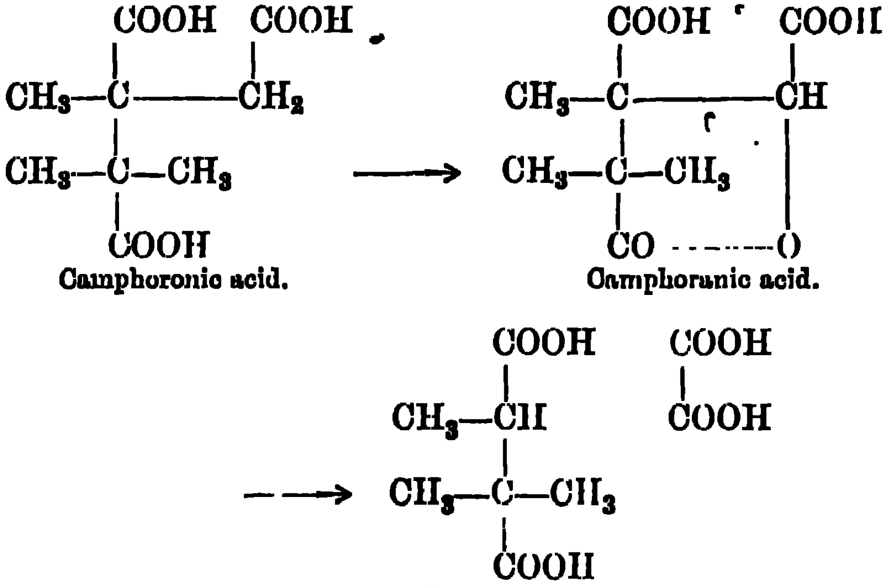
[1] Perkin and Thorpe, *Trans. Chem. Soc.*, 1897, 71, 1169.



Camphoronic acid.

Camphoranic acid.

Trimethylsuccinic and oxalic acids.

6. *Camphene.*

Camphene, $C_{10}H_{16}$, is a hydrocarbon isomeric with bornylene; but its constitution is still one of the enigmas of organic chemistry. It would occupy too much space were we to weigh the pros and cons of all the formulæ which have been proposed for the compound; and in the present section we can do little more than indicate the difficulties with which the problem is surrounded.[2]

In the first place, we may give two of the methods by which the hydrocarbon can be produced,* as these show how complex the question is, even in its earliest stages.

Berthelot[3] prepared it by heating pinene hydrochloride or hydrobromide with sodium stearate to 200°–220° C. Wallach[4] obtained it by dehydrating borneol with potassium bisulphate at 200° C. or by heating bornyl chloride with aniline. We already know that bornylene contains the skeleton (I.), and as we shall see later the pinene molecule contains the skeleton (II.),

---

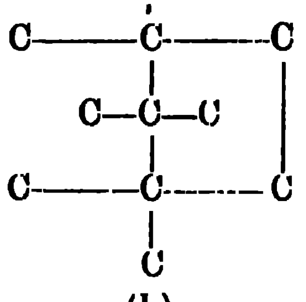
[1] Bredt, *Annalen*, 1898, **299**, 150.

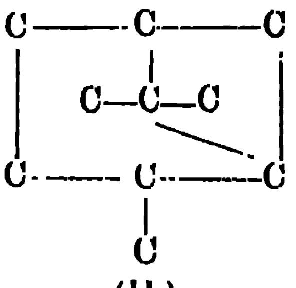
[2] For recent discussions of camphene's structure see Aschan, *Annalen*, 1910, **375**, 336; Lipp, *ibid.*, 1911, **382**, 265; Henderson and Heilbron, *Trans.*, 1911, **99**, 1901.

* Crude "camphene" appears to contain materials other than pure camphene (Aschan, *Annalen*, 1910, **375**, 336).

[3] Berthelot, *Compt. rend.*, 1862, **55**, 496.

[4] Wallach, *Annalen*, 1885, **230**, 233, 239.


(I.)


(II.)

so that even at this stage some intramolecular change must be assumed during the formation of camphene from one or other of these groupings. Once the camphene skeleton is formed, it is extremely stable. Those reagents which usually produce intramolecular rearrangement act upon it only at high temperatures, and their effect is to bring about deep-seated changes in its structure.

When camphene is treated with bromine, the first reaction appears to be an addition of one molecule of the halogen; but this is immediately followed by a separation of hydrobromic acid, leaving a mono-bromocamphene.[1] By further action of bromine or by brominating camphene in ligroin solution at −10° C., a halogen addition product, camphene dibromide,[2] is obtained which has the composition $C_{10}H_{16}Br_2$. A tribromide, $C_{10}H_{16}Br_3$ has also been obtained, which is probably formed partly by substitution and partly by addition.

Concentrated nitric acid forms with camphene an addition product containing equimolecular quantities of the two reagents.[3]

Hydrochloric acid acts upon camphene giving the chloride of an alcohol, isoborneol; whilst a mixture of sulphuric acid and acetic acid produces with camphene the acetate of the same alcohol.[4]

---

[1] Wallach, *Annalen*, 1885, **230**, 233.

[2] Reychler, *Ber.*, 1896, **29**, 900.

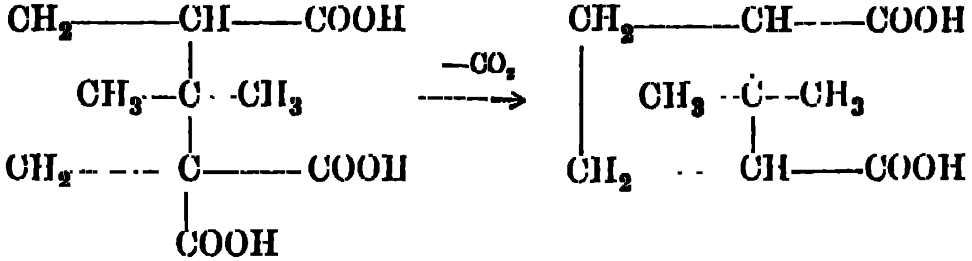
[3] Bouveault, *Bull. soc. chim.*, 1900, (3), **23**, 533.

[4] Bertram and Wahlbaum, *J. pr. Chem.*, 1894, (2), **49**, 8.

By the action of nascent nitrous acid upon camphene,[1] three compounds are simultaneously formed: camphene nitronitrosite, $C_{10}H_{16}(NO_2)_2$. NO; camphene nitrosite, $C_{10}H_{16}$. (NO_2) . NO; and camphenylnitrite, $C_{10}H_{15}$. O . N : O. When the last compound is heated with potassium hydroxide solution it yields a ketone, camphenilone, $C_9H_{14}O$; whilst on reduction it produces camphenilan aldehyde, C_9H_{15} . CHO. The same aldehyde is formed from camphene by the action of chromyl chloride and hydrolysis with water.[2]

Oxidation of camphene with alkaline permanganate[3] produces an 80 per cent. yield of camphenic acid.

When nitric acid[4] is substituted for permanganate, the first product isolated is camphoic acid, a tribasic acid which on heating loses carbon dioxide and produces apocamphoric acid. This reaction recalls the behaviour of malonic acid; and the constitution of camphoic acid is therefore assumed to be that which is shown below:—



Camphoic acid. Apocamphoric acid.

Camphoic acid is also obtained by the oxidation of dihydrocamphene.[5]

Henderson and Sutherland[6] obtained, among the oxidation products of camphene, iso-camphenilan aldehyde (supposed to be a stereoisomer of camphenilan aldehyde), camphenilone, and an acid $C_{10}H_{16}O_2$, isomeric with iso-camphenilanic acid, into which it is transformed by heating with acetic anhydride. When acted upon by chromic acid, camphene is converted into camphor.[1] The ozonide of camphene yields on decomposition formaldehyde, camphenilone, and dimethyl-norcampholide.

---

[1] Jagelki, *Ber.*, 1899, **32**, 1501.
[2] Bredt and Jagelki, *Annalen*, 1900, **310**, 112.
[3] Haworth and King, *Trans.*, 1912, **101**, 1975.
[4] Marsh and Gardner, *Trans.*, 1891, **59**, 64; 1896, **69**, 74.
[5] Lipp, *Annalen*, 1911, **382**, 265.
[6] Henderson and Sutherland, *Trans.*, 1911, **99**, 1539.

Finally, Henderson and Pollock[2] have shown that when camphene is reduced by Sabatier and Senderens' method it yields, not camphane, but an isomeric hydrocarbon.

We must now see how far this evidence takes us.

In the first place, it is clear that the syntheses of camphene throw no great light upon its constitution. Either the production of camphene from borneol or its formation from pinene hydrochloride must entail a molecular rearrangement, since these substances do not contain the same skeleton; and it is not impossible that both reactions are attended by intramolecular change.

The reaction between camphene and bromine brings us a stage further. Ethylene derivatives sometimes react in this way, when at least one of the carbon atoms joined by the double bond carries a hydrogen atom. Further, the ready action of the halogen in the case of camphene leads to the conclusion that it probably contains some grouping such as $R_2 : C : CH_2$ or $R_2 : C : CHR$; since these are more readily attacked than the parent hydrocarbon. The possibility that the action of bromine is due to the presence of an easily-opened polymethylene ring in the camphene structure appears to be negatived by the reaction between the hydrocarbon and nitrous acid, which implies the presence of an ethylenic bond.

The behaviour of camphenyl nitrite with caustic potash points to its probably having the structure $C_9H_{14} : CH . O . N : O$; which would indicate that camphene itself contains the group $R_2C : CH_2$.

It is now necessary to gain information with regard to the position of the two methyl groups; and the syntheses of camphenic acid[3] and dimethyl-norcampholide[4] supply the required material. From the structures of these compounds shown below it will be seen that the two methyl groups are attached to a carbon atom outside the pentamethylene ring.

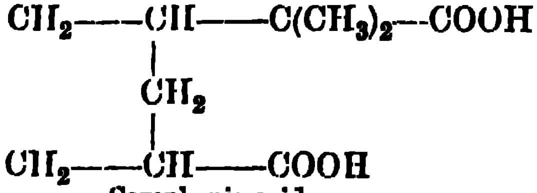
---

[1] Armstrong and Tilden, *Ber.*, 1879, **12**, 1756.

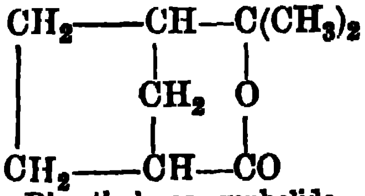
[2] Henderson and Pollock, *Trans.*, 1910, **97**, 1620; compare Lipp, *Annalen*, 1911, **382**; 265.

[3] Lipp, *Ber.*, 1914, **47**, 871.

[4] Komppa and Hintikka, *Ber.*, 1909, **42**, 898.

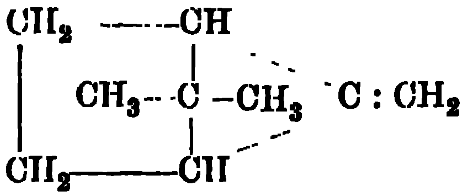


Camphonic acid.



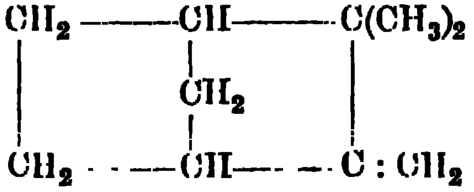
Dimethyl-norcampholide.

This evidence excludes the Semmler formula for camphene :—



since in it there is no five-membered ring free from the dimethyl part of the molecule ring.

So far, then, the experimental evidence points towards the Wagner formula:—



but it must be admitted that even this formula will not fit all the facts. It is difficult to see how the production of camphenic acid can be accounted for directly.

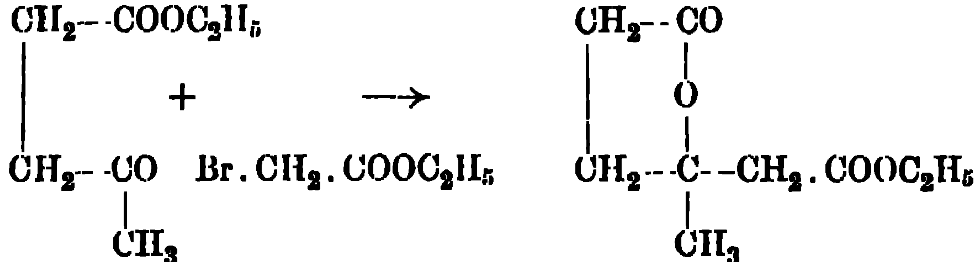
The only solution is to assume that intramolecular changes occur in the camphene molecule under the action of various reagents; and, as will be seen in the last section of this chapter, some such intramolecular rearrangements must be postulated if the behaviour of this group of terpenes is to be explained in a satisfactory manner.

B.—Fenchene and its Derivatives.

1. *The Syntheses of Fenchone and Fenchyl Alcohol.*

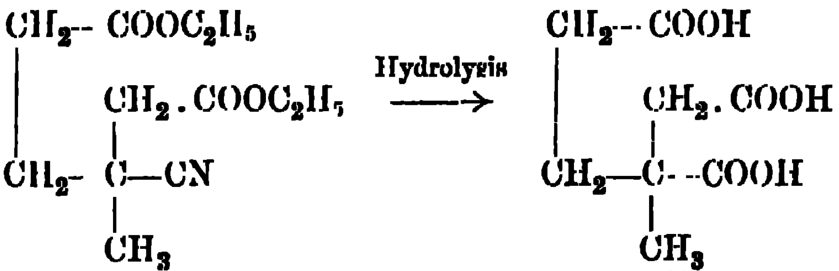
Until quite recently, the exact constitution of fenchone had not been placed beyond doubt; for its degradation products are labile and difficult to utilize in the problem of determining the structure of the parent substance. A synthesis of the substance has now been attained, however, which establishes its constitution.[1]

The actual synthesis starts from lævulinic ester and bromacetic ester which are condensed together by means of zinc—



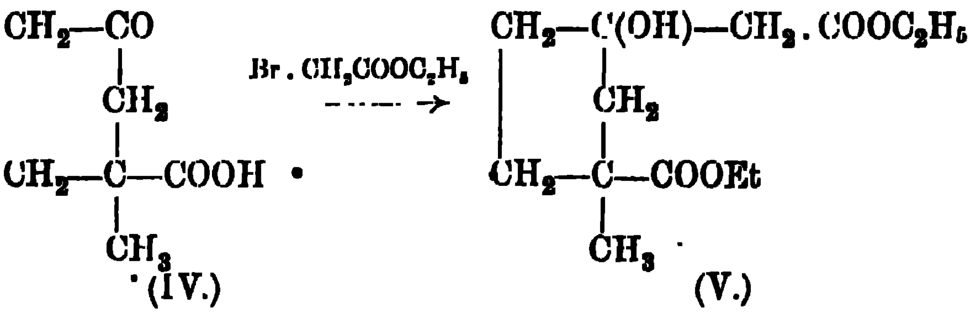
(I.)

The lactonic ester (I.) thus formed is heated with potassium cyanide, which converts it into the nitrile (II.). Hydrolysis yields the tricarboxylic acid (III.).



(II.) (III.)

On heating with sodium and benzene, this substance forms a pentamethylene derivative (IV.); and when the ethyl ester of this is condensed with α-bromoacetic ester in presence of zinc, a new chain is added, as shown in (V.). This compound apparently loses water and forms (VI.); for the reaction mixture contains both materials—



(IV.) (V.)

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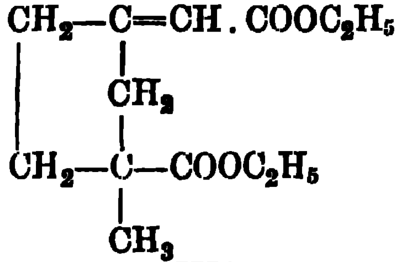
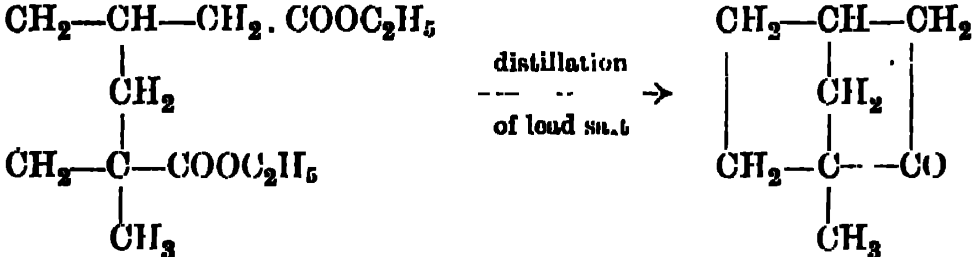
[1] Ruzička, *Ber.*, 1917, 50, 1362.

and



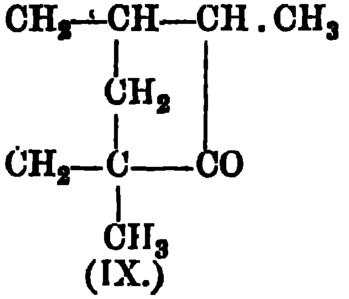
(VI.)

The mixture is treated with phosphorus tribromide in chloroform, which converts it all into (VI.); and then the ester is reduced to (VII.). The lead salt of this breaks down on distillation in the usual manner, forming the internal ketone, methyl*nor*camphor (VIII.).

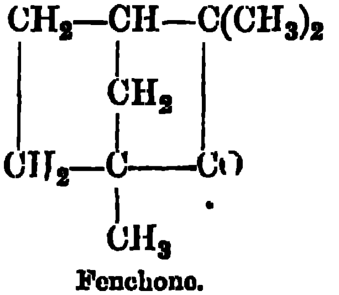


(VII.) (VIII.)

Methylation by means of sodamide and methyl iodide completes the process, producing a mixture of fenchosantenone (IX.) and racemic fenchone—



(IX.)



Fenchone.

This synthesis proves the correctness of the formula proposed for fenchone by Semmler.[1]

Reduction of fenchone produces fenchyl alcohol, which must therefore have the following structure :—

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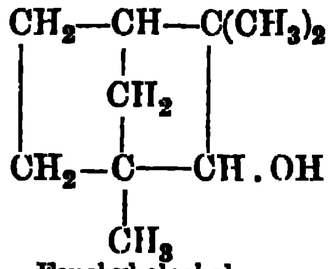
[1] Semmler, *Ch. Ztg.*, 1905, **29**, 1313; compare Bouveault and Levallois, *Compt. rend.*, 1908, **146**, 180.



Fenchyl alcohol.

2. *The Decompositions of the Fenchenes.*

For a long time the structures of the fenchenes were a puzzle to organic chemists. As we have seen, the reduction of fenchone yields fenchyl alcohol. It is found that *d*-fenchone gives rise to a lævo-rotatory alcohol, which is therefore described as D-*l*-fenchyl alcohol. When this is treated with phosphorus pentachloride at a low temperature it gives D-*l*-fenchyl chloride which, with aniline, loses hydrochloric acid and yields D-*l*-fenchene. This compound is now known as *α*-fenchene.[1]

If phosphorus pentachloride be allowed to act on fenchyl alcohol without cooling, a dextro-rotatory chloride is formed, which on treatment with aniline, produces D-*d*-fenchene, or *β*-fenchene. It is also possible to prepare *β*-fenchene by heating fenchyl alcohol with potassium hydrogen sulphate.[2]

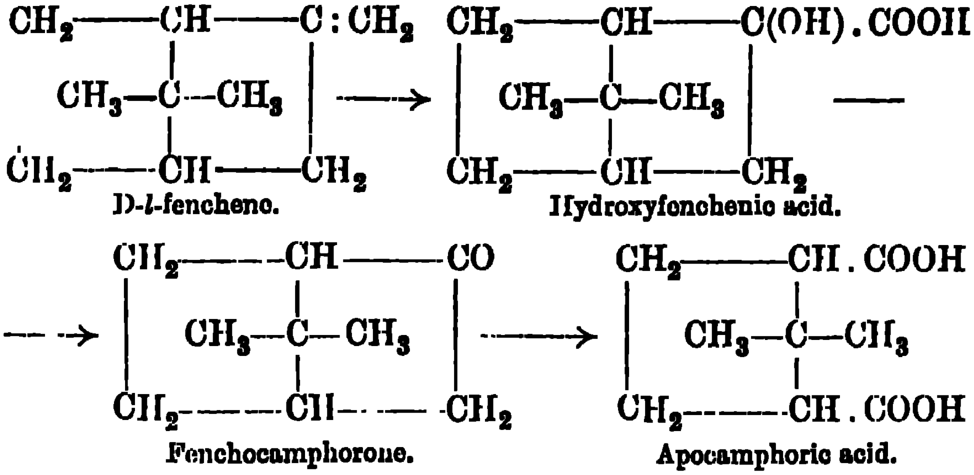
The constitution of D-*l*-fenchene (*α*-fenchene) has been dealt with in the following way.[3] When it is oxidized with potassium permanganate it is converted into a hydroxy-acid, D-*l*-hydroxy-fenchenic acid, which has the composition $C_{10}H_{16}O_3$. This body, when treated with lead peroxide and sulphuric acid, loses carbon dioxide and two atoms of hydrogen, being converted into D-*d*-fenchocamphorone, $C_9H_{14}O$. By nitric acid this last compound is broken down to apocamphoric acid. This production of apocamphoric acid from fenchene shows that in fenchene itself one of the carbon atoms must be attached to the nucleus at a point different from that at which the methyl group in camphor is placed; as otherwise we should find camphoric acid produced in the end instead of its next lower homologue, apocamphoric acid. The only way in which we can satisfy this requirement is shown in the formulæ below—

---

[1] Kommpa and Roschier, *Ann. Acad. Sci. fennicae*, 1915, (A), 7, No. 14, 1.

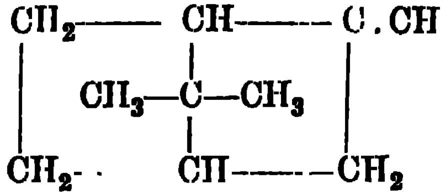
[2] *Ibid.*

[3] Wallach, *Annalen*, 1898, 300, 294; 1901, 315, 283.



D-*l*-fenchene. Hydroxyfenchenic acid. Fenchocamphorone. Apocamphoric acid.

D-*l*-fenchene, therefore, has the constitution expressed by—



How such a structure can arise by the dehydration of fenchyl alcohol or the removal of a molecule of hydrochloric acid from fenchyl chloride, is one of the puzzles of organic chemistry; and the matter is not made simpler by the occurrence of the second fenchene isómer.

With regard to the constitution of this β-fenchene, very little is known.[1] When prepared from racemic fenchyl alcohol and sodium hydrogen sulphate, it forms part of a mixture of hydrocarbons from which it can be separated by distillation. The pure product, on oxidation with alkaline permanganate, yields *r*-hydroxy-β-fenchenic acid, isomeric with hydroxyfenchenic acid. Further oxidation, with acid permanganate, gives *r*-β-fenchocamphorone, isomeric with fenchocamphorone; and a final oxidation, this time with alkaline permanganate, produces a dibasic acid, $C_9H_{14}O_4$, an isomer of apocamphoric acid. This last compound gives no anhydride, which may point to it being a *trans*-compound. Beyond that, nothing is known of its structure.

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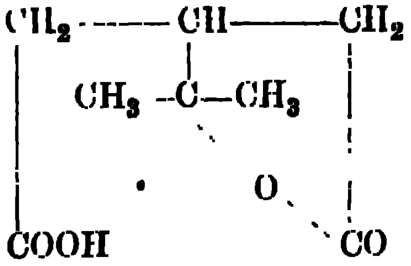
[1] Komppa and Roschier, *Ann. Acad. Sci. fennicæ*, 1916, (A), 7, No. 14, 1.

C.—PINENE.

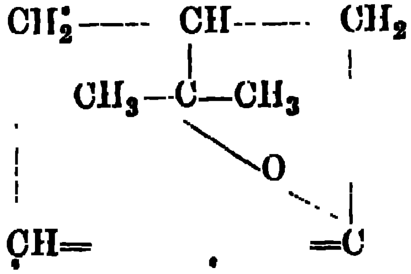
1. *The Constitution of Pinene.*

Pinene is a hydrocarbon isomeric with camphene and fenchene. It was found by Sobrero[1] that when this substance was allowed to stand in sunlight in contact with water and air it was, after several months, converted into a compound sobrerol,* $C_{10}H_{16}(OH)_2$, which, on boiling with dilute acids, was changed, by the loss of one molecule of water, into pinol, $C_{10}H_{16}O$. Pinol was found, on further investigation, to be an internal ether of the same type as cineol. Wallach[2] has shown that pinol may also be obtained by the action of sodium ethylate on terpineol dibromide.

When pinol or sobrerol is treated with a 1 per cent. solution of potassium permanganate the product is a dihydric alcohol[3] pinol-glycol, $C_{10}H_{16}O(OH)_2$. On further oxidation, a tetrahydric alcohol[4] sobrerythrite, $C_{10}H_{16}(OH)_4$, is formed, which in turn is oxidized to terpenylic acid. Therefore we should find in pinene, pinol, and pinol-glycol, the same chain of carbon atoms which we know exists in terpenylic acid—



In other words, the pinol skeleton must contain the grouping—



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[1] Sobrero, *Annalen*, 1861, **80**, 106.

* Sobrerol can also be obtained by acting on pinene with mercuric acetate (Henderson and Agnew, *Trans.*, 1909, **95**, 289).

[2] Wallach, *Annalen*, 1890, **259**, 309.

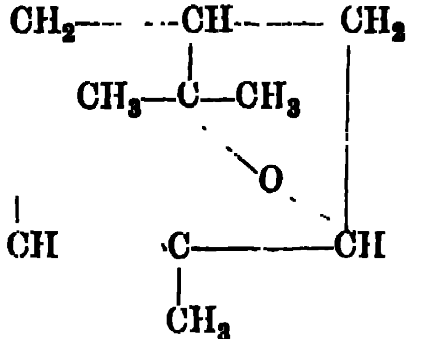
[3] Wagner and Slawinski, *Ber.*, 1894, **27**, 1644.

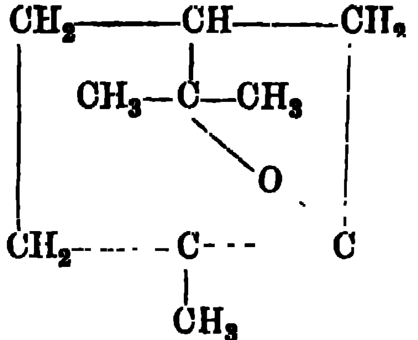
[4] Wagner and Ginsberg, *Ber.*, 1894, **27**, 1648; 1896, **29**, 1195.

Into this scheme we have now to fit a hydrogen atom and the group—

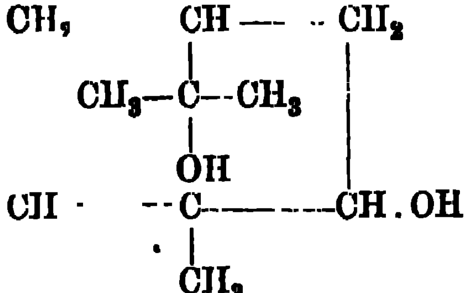
$$CH_3-\underset{|}{C}:$$

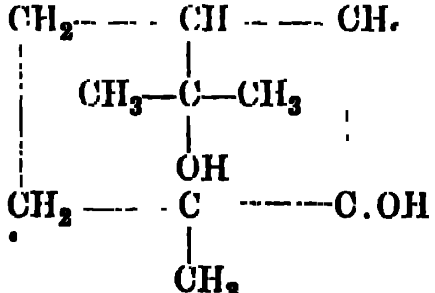
and, as can at once be seen, there are two possible ways of doing this—


Pinol I.

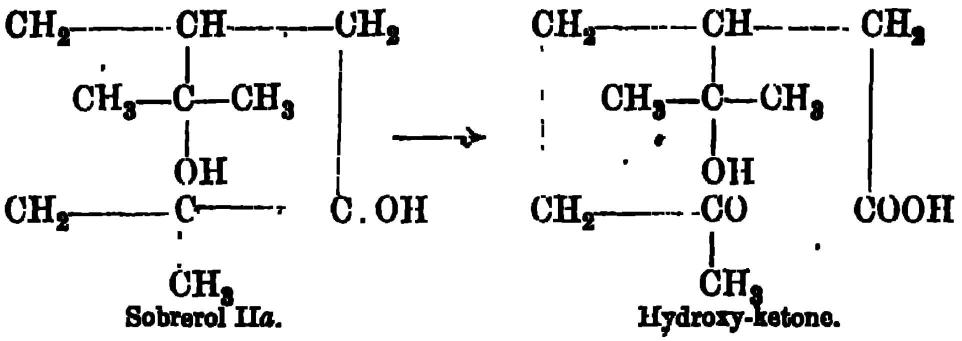

Pinol II.

On these two assumptions sobrerol, which is obtained from pinol by the addition of water, would have either of the formulæ—


Sobrerol Ia.

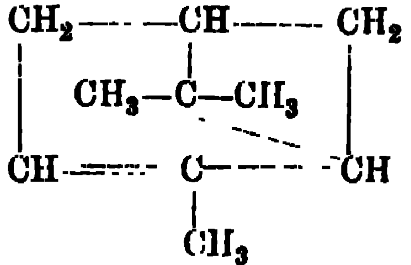

Sobrerol IIa.

Now, sobrerol, on oxidation with a 1 per cent. solution of potassium permanganate, gives a tetrahydric alcohol, sobrerythrite. This can only be explained by using the formula (*Ia.*), for (*IIa.*) would produce a hydroxy-ketone—


Sobrerol IIa. Hydroxy-ketone.

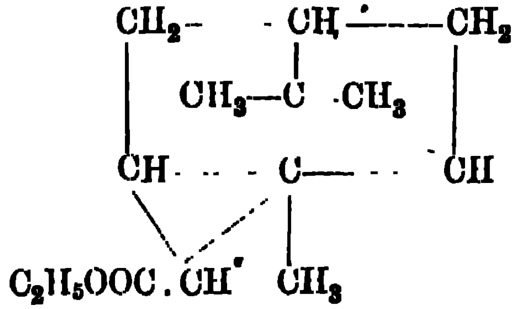
Sobrerol, therefore, has the formula (I*a*.) and pinol the formula (I.).

From this we may conclude that the formula of pinene itself is—



Pinene.

Further evidence in support of this constitution is supplied by the behaviour of pinene with diazo-acetic ester. It is well known that the latter body interacts with compounds containing ethylenic bonds to produce pyrazolin derivatives, which then decompose, yielding trimethylene compounds.[1] Now when pinene and diazo-acetic ester interact, the end-product is a substance of the following structure[2]:—



and since we know that the ring is formed partly from the two atoms between which the double bond originally existed, this tends to establish the pinene formula which was deduced above.

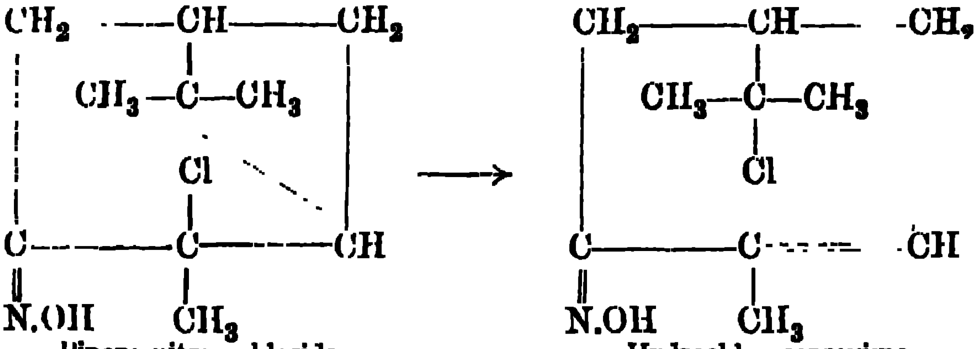
In virtue of the double bond in its molecule, pinene is capable of uniting with hydrochloric acid or nitrosyl chloride. Pinene hydrochloride resembles camphor in appearance and smell, and is used commercially under the name of "artificial camphor." Pinene nitrosochloride,[3] on standing in presence of hydrochloric acid, is converted into hydrochlorocarvoxime by the wandering of a chlorine atom and the rupture of the pinene tetramethylene ring—

---

[1] Buchner and Curtius, *Ber.*, 1885, 18, 237.

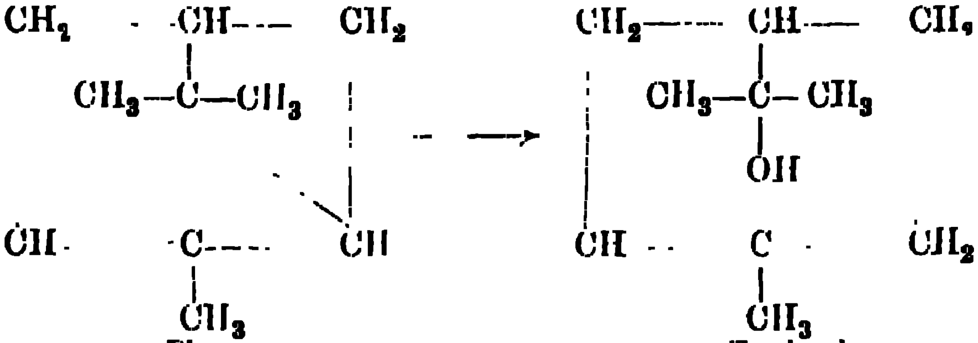
[2] Buchner and Rehorst, *Ber.*, 1913, 46. 2680, 2687.

[3] Baeyer, *Ber.*, 1896, 29, 20.



Pinene nitrosochloride. Hydrochlorocarvoxime.

Pinene itself is converted into terpineol by hydration with dilute acids—



Pinene. Terpineol.

2. *Pinonic and Pinic Acids.*

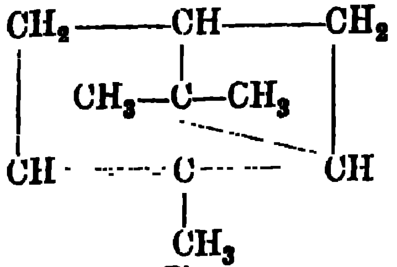
When pinene is oxidized with potassium permanganate, the first product is a ketonic acid[1] which, according to the conditions of the experiment, can be obtained either as a single substance or as a mixture of two isomers. When the single substance is produced it is found to have the composition $C_{10}H_{16}O_3$, and has been named *a*-pinonic acid. It contains the group CH_3-CO-, for, on treatment with bromine and potash, it loses a methyl group, takes up hydroxyl, and is converted into pinic acid, $C_9H_{14}O_4$—

$$\underset{\text{Pinonic acid.}}{C_8H_{13}O_2\text{—CO—}CH_3} \xrightarrow{\text{KOH and Br}} \underset{\text{Pinic acid.}}{C_8H_{13}O_2\text{—COOH}} + CHBr_3$$

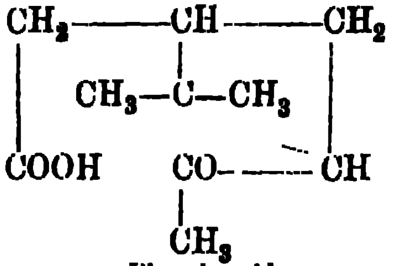
---

[1] Baeyer, *Ber.*, 1896, **29**, 3.

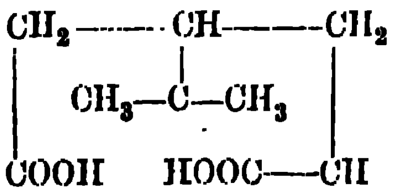
These changes are expressed in the following formulæ:—



Pinene.

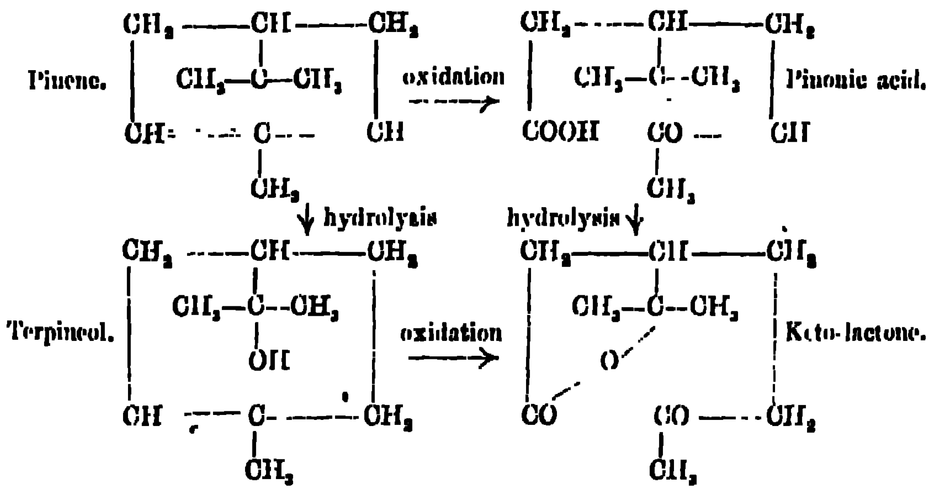


Pinonic acid.



Pinic acid.

Now, on hydrolysis with 50 per cent. sulphuric acid, pinonic acid gives a keto-lactone,[1] $C_{10}H_{16}O_2$, which proves to be identical with that obtained in the oxidation of terpineol. A similar hydrolysis converts pinene into terpineol, so that the following scheme shows the relations between the four substances:—



D.—INTRAMOLECULAR REARRANGEMENTS IN THE DICYCLIC TERPENES.

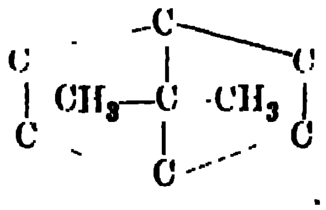
It has already been pointed out in the course of this chapter that some of the reactions in the dicyclic terpene group cannot be satisfactorily represented without the aid of assumed intramolecular changes. Some suggestions as to the nature of such changes have been made by Aschan[1] and Meerwein;[2] while Collie[3] has worked out a more complete scheme with which we may now deal.

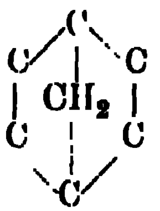
---

[1] Baeyer, *Ber.*, 1896, 29, 3.

In order to account for the intramolecular changes proposed, three assumptions are made. In the first place, it is assumed that a trimethylene ring may be formed or ruptured within the molecule. Secondly, it is postulated that a dicyclic compound containing two five-membered rings is more stable than an isomer which contains one four-membered and one six-membered ring. Thirdly, the suggestion is made that the grouping (I.) is preferred to (II.) in the course of intramolecular changes.

(I.)





(II.)

Now let us take the changes in the camphene series as a starting-point. The scheme of these is given on p. 83. The first set are concerned with the conversion of pinene hydrochloride into camphene. It will be noticed that the initial step depends upon the third assumption and consists in a rearrangement of the grouping (II.) into the grouping (I.), which is accompanied by a wandering of the chlorine atom from one carbon atom to the next. The next two stages represent the splitting off of hydrochloric acid with the formation of a trimethylene ring and the subsequent readdition of the acid in a new position to give two pentamethylene rings. Finally, by the elimination of hydrochloric acid, camphene is formed, which may be represented either according to the Wagner formula or with a trimethylene ring in its system, these two structures being assumed to be mutually interchangeable.*

The second series of rearrangements is based upon this view of the duality of the camphene structure. The trimethylene ring variety gives rise to camphenic acid; whilst the Wagner formula leads to camphenilone.

---

[1] Aschan, *Annalen*, 1912, 387, 1.

[2] Meerwein, *ibid.*, 1914, 405, 129.

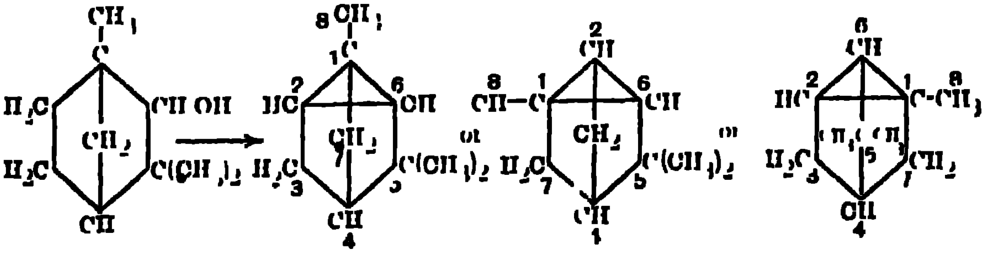
[3] Collie, private communication.

* For a somewhat parallel rearrangement, compare the conversion of dihydrocarvone into carone or the change of carylamine into vestrylamine, etc.

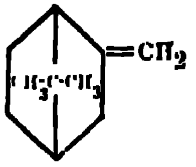
The production of camphoic acid and apocamphoric acid is dealt with in the third series. In this case, the first step is the production of a hydroxy-acid by the gentle oxidation of the double bond in the camphene molecule. Then follows the elimination of water and the formation of a trimethylene ring. By the readdition of water, this trimethylene ring is opened; and the fission takes a form which brings into existence the grouping (I.) instead of the grouping (II.). Finally, oxidation gives rise to camphoic and apocamphoric acids.

The fourth series of changes shows the conversion of camphene into bornyl alcohol. The first step is the addition of a molecule of water. Then follows elimination of water from a different pair of positions, with the production of the trimethylene ring. The next formula is identical but is merely written in a different form. Finally, the trimethylene ring is ruptured by the addition of water and bornyl alcohol is produced.

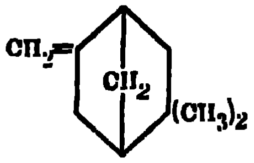
Let us now turn to the fenchene series. Collie symbolises the conversions in the following manner. Assume in the first place that fenchyl alcohol loses water in such a way as to form a trimethylene ring within the molecule. The resulting compound may be written in three different ways which are structurally identical:



Now if hydrochloric acid be added on to the molecule in such a way as to break the bond between the carbon atoms numbered 2 and 6, fenchyl chloride will be formed. If, however, the trimethylene ring breaks between the atoms 1 and 6 and rearrangement into a double bond takes place instead of reformation of the trimethylene grouping, then either α- or β-fenchene may be produced.

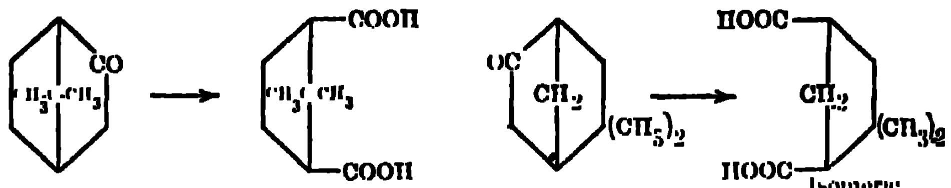


α-fenchene



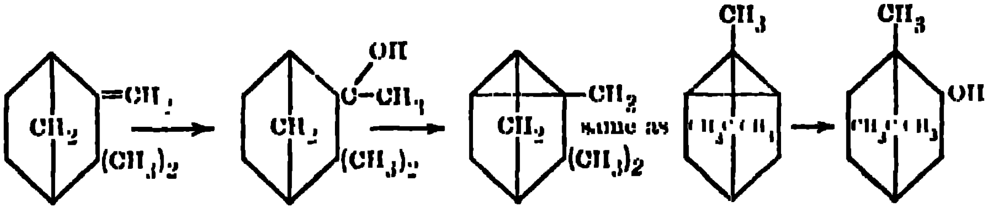
β fenchene

The production of apocamphoric acid from α-fenchene and the oxidation of β-fenchene to an isomeric apocamphoric acid are thus symbolised by Collie:



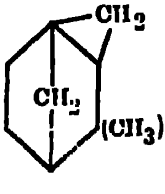
α fenchocamphorone Apocamphoric Acid β fenchocamphorone Isomeric Apocamphoric Acid

The change of camphene into bornyl alcohol may be accounted for thus:



Camphene Bornyl Alcohol

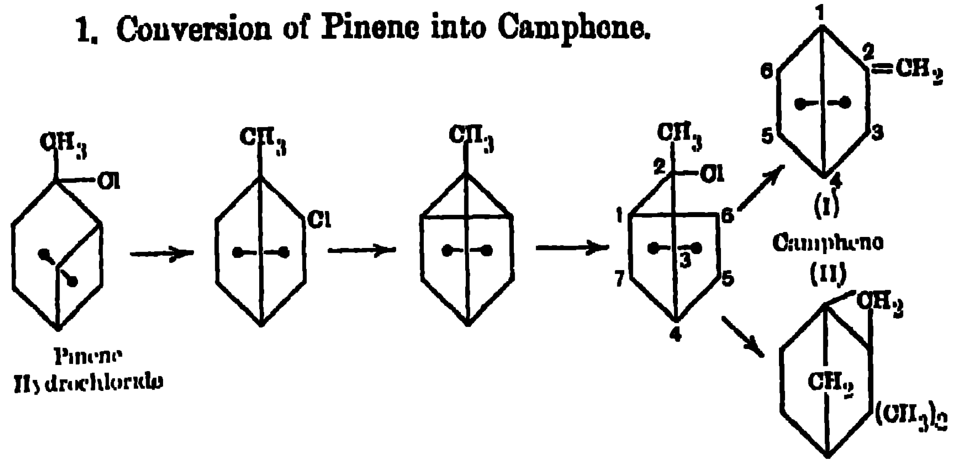
It should be noted that on Collie's view camphene and the two fenchenes may all be tautomeric forms of a fourth structure which contains a trimethylene grouping.



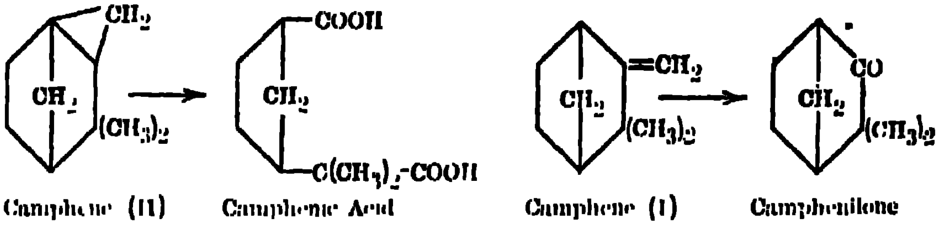
CAMPHENE'S REACTIONS.

(NOTE: The symbol •—·—• is used to represent CH_3—C—CH_3 inside the hexagon.)

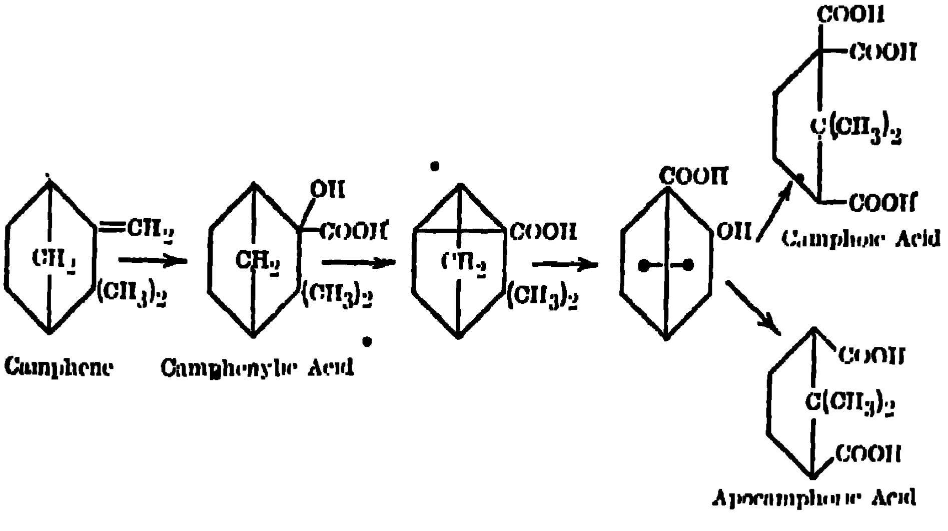
1. Conversion of Pinene into Camphene.



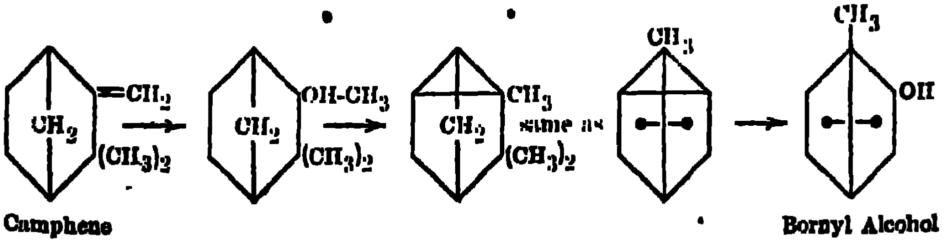
2. Formation of Camphenic Acid and Camphenilone.



3. Camphoic Acid and Apocamphoric Acid from Camphene.



4. Production of Bornyl Alcohol from Camphene.



CHAPTER IV

THE OLEFINIC TERPENES

A.—INTRODUCTION

We have now described the most important cyclic terpenes, and we must next examine the olefinic substances which are often included in the terpene group. It might have been more logical to have dealt with the open-chain compounds first, and the cyclic ones later, but as we should in that case have had to assume the constitution of certain cyclic terpenes which are closely connected with the olefinic ones, the present method of arrangement is more convenient.

Those unsaturated open-chain substances which are found in ethereal oils, and which, in many cases, can be transformed into cyclic terpenes, are termed olefinic terpenes, or terpenogens. They occur as hydrocarbons, aldehydes, or alcohols, and are derived from hydrocarbons of the formula C_5H_8. In many cases the odour of ethereal oils is very largely due to the olefinic terpenes contained in them.

The chemical importance of the olefinic terpenes lies in the fact that from them we can build up some of the more complicated terpene derivatives by means of very simple reactions; but they are of interest also from the commercial point of view as forming the basis of many natural and artificial perfumes.

B.—ISOPRENE.

Isoprene is the simplest of all the olefinic terpenes; it contains two double bonds, and has the composition C_5H_8. Its synthesis has been carried out by Euler,[1] and also by Ipatjew,[2] in the one case starting from methyl-pyrrolidine, and in the other from dimethyl-allene. In the first case, the methyl-pyrrolidine (I.) is allowed to interact with methyl iodide with the formation of dimethyl-methylpyrrolidinium iodide (II.). This substance is then decomposed with potash, whereby the ring is broken and *des*-dimethyl-methylpyrrolidine (III.) is produced. The addition of methyl iodide and decomposition of the product (IV.) with potash gives trimethylamine and the required isoprene (V.)—

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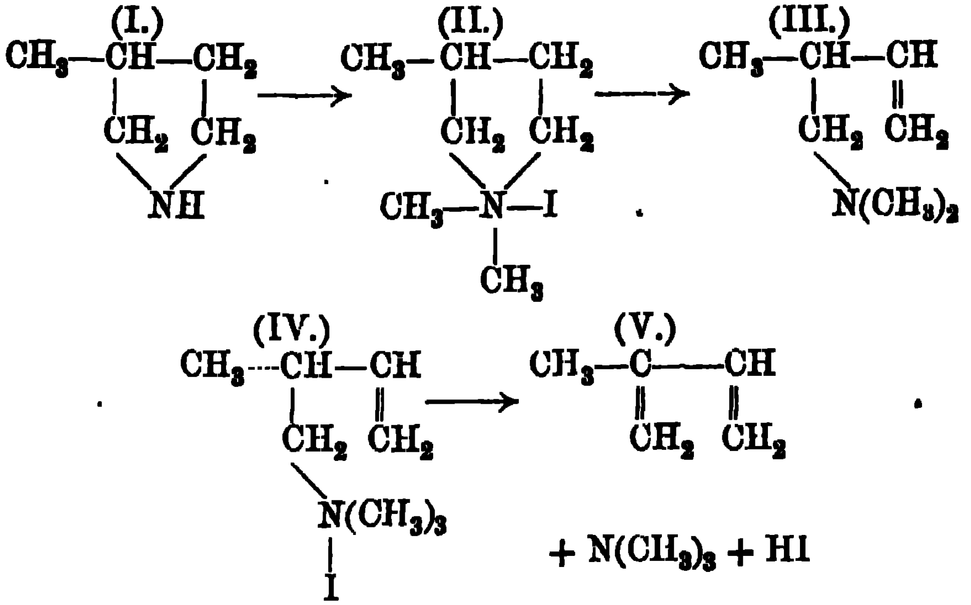
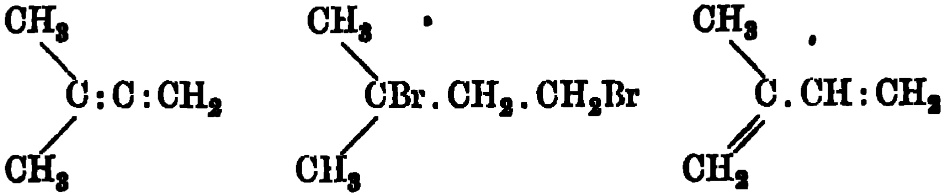
[1] Euler, *J. pr. Chem.*, 57, 132.

[2] Ipatjew, *ibid.*, 55, 4.



The synthesis from dimethyl-allene is much simpler. Two molecules of hydrobromic acid are added on, forming 2-methyl-2, 4-dibromobutane, from which hydrobromic acid is again split off by means of alcoholic potash—

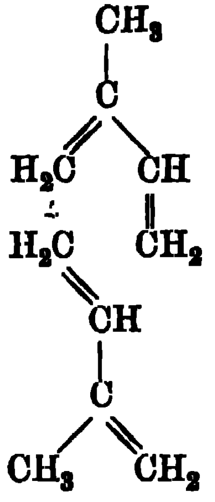


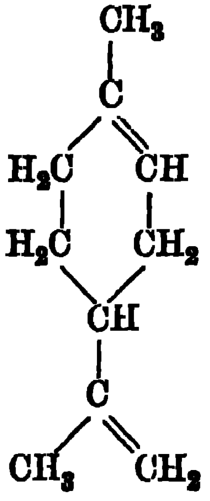
Dimethyl allene. Methyl-dibromobutane. Isoprene.

Isoprene is produced by the dry distillation of indiarubber and by the decomposition of turpentine oil at a dull red heat. Concentrated hydrochloric acid converts it into a polymer which has all the physical properties of indiarubber, and the same change takes place on long standing or with traces of acids in sunlight. When heated to 300° C., isoprene is polymerized to a di-isoprene,[1] which seems to be identical with dipentene—

---

[1] Tilden, *Trans. Chem. Soc.*, 1884, **45**, 410; Bouchardat, *C. R.*, 1875, **80**, 1440; 1878, **87**, 654; 1879, **89**, 361, 1117.



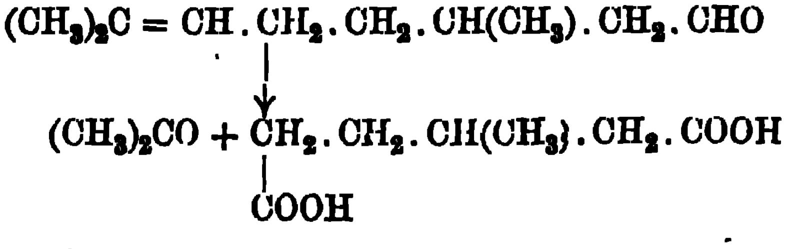


In a somewhat similar manner isoprene might be supposed to give a sesquiterpene in which three isoprene molecules would coalesce to form a compound of the composition $C_{15}H_{24}$. In any probable reaction of this type, it is worth noting, at least one unsaturated chain will be left untouched and ready to react with further molecules if the proper conditions are obtained; and it is doubtless to this side chain that we owe the more complex polymer which resembles indiarubber.

C.—CITRONELLAL.

We must now pass to the consideration of a substance rather more complicated than isoprene—the compound citronellal, which was discovered by Dodge[1] in citronella oil. Citronellal is an aldehyde, for on reduction it gives the alcohol citronellol, and on oxidation it forms citronellic acid. Since it is optically active it must contain an asymmetric carbon atom.

Tiemann and Schmidt,[2] oxidizing it in *aqueous* solution, obtained as products acetone and β-methyl-adipic acid, from which they concluded very naturally that citronellal had the constitution—



$$\begin{array}{l}(CH_3)_2C = CH.CH_2.CH_2.CH(CH_3).CH_2.CHO \\ \qquad\qquad\quad\downarrow \\ (CH_3)_2CO + \underset{\displaystyle COOH}{CH_2}.CH_2.CH(CH_3).CH_2.COOH\end{array}$$

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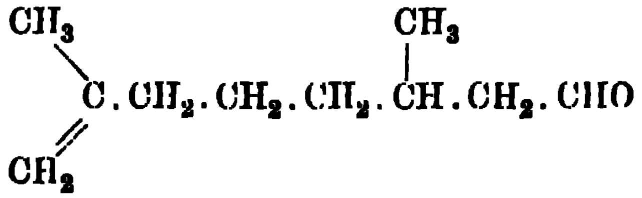
[1] Dodge, *Am. Chem. J.*, 1889, **11**, 456.

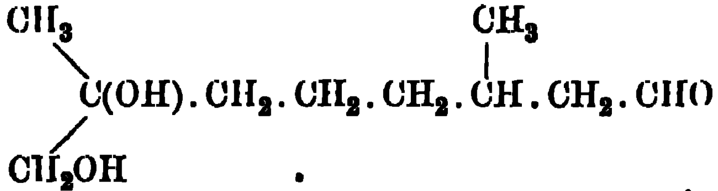
[2] Tiemann and Schmidt, *Ber.* 1896, **29**, 903; 1897, **30**, 22, 33.

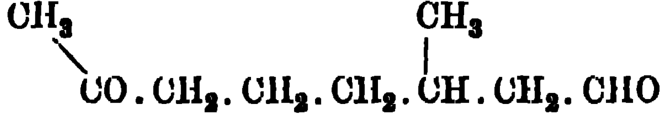
The reason for placing the methyl group in this position will be seen later when we deal with the production of pulegone from this body.

This constitution, however, is not in agreement with the work of Harries and Schauwecker,[1] who approached the matter from a slightly different standpoint. Instead of oxidizing citronellal itself, they prepared its dimethyl-acetal and replaced the aqueous solution of Schmidt and Tiemann by an acetone one. Under these circumstances they found that the oxidation product with potassium permanganate was the acetal of a dihydroxy-dihydrocitronellal, which, on further oxidation with chromic acid, could be converted into a keto-aldehyde. This shows that the double bond must lie at the extreme end of the chain, so that citronellal would have the constitution—



On this view the dihydroxy-compound and the keto-aldehyde would be—





The results obtained by Tiemann and Schmidt would be explained by supposing that under the influence of the aqueous oxidizing agent the position of the double bond was changed from the ultimate to the penultimate pair of carbon atoms in the chain.

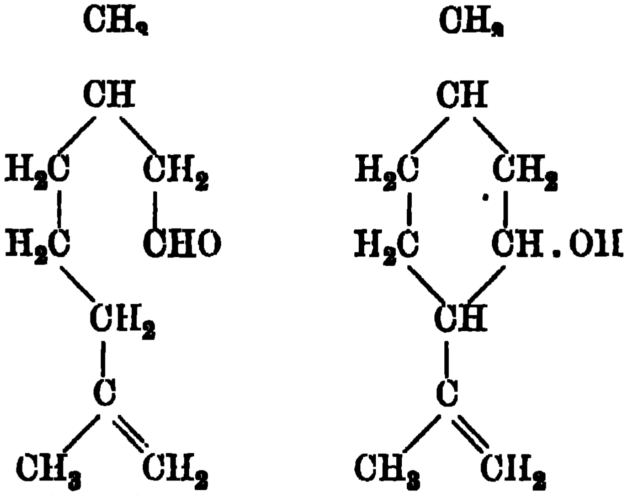
So far we have not proved the position of the methyl group, but we shall now give some evidence bearing upon the point. When citronellal is allowed to stand by itself for a considerable time it is converted into the isomeric substance isopulegol.[2]

---

[1] Harries and Schauwecker, *Ber.*, 1901, **34**, 1498, 2981.

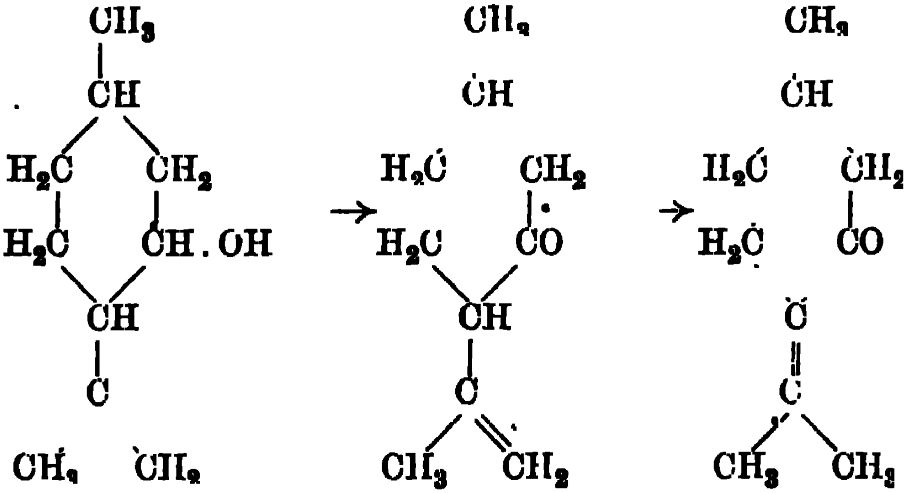
[2] Labbe, *Bull. soc. chim.*, 1899, [iii.], **21**, 1023.

The same change is brought about more rapidly by heating citronellal with acetic anhydride[1] to 180° C. The change may be represented in the following manner:—



Citronellal. Isopulegol.

The proof of the constitution of isopulegol depends upon its conversion into pulegone. When it is oxidized it yields the ketone isopulegone, which is converted into pulegone by the wandering of the double bond—



Isopulegol. Isopulegone. Pulegone.

From this it is evident that the methyl group in citronellal must be in the position which we attributed to it; as otherwise the isopropylene group would not come into the 1, 4-position with it in the pulegone formed from citronellal.

We may postpone the consideration of the alcohol citronellol and of citronellic acid until later, as they are closely connected with some members of the class of compounds with which we are about to deal in the next section.

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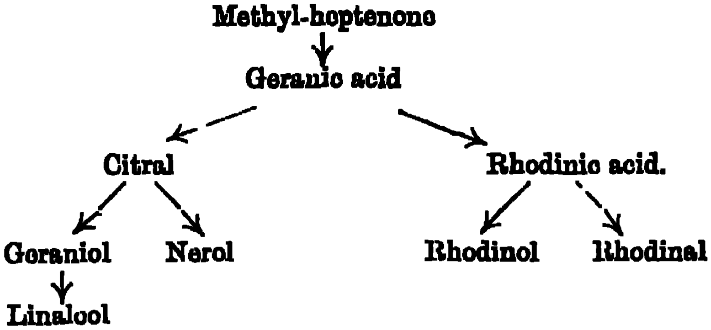
[1] Tiemann and Schmidt, *Ber.*, 1896, **29**, 913; **30**, 27.

D.—The Citral Group.

1. *General.*

The group of olefinic terpenes, of which citral is the most important member, can all be derived from the unsaturated ketone methyl-heptenone. It will perhaps be best, before entering upon a detailed consideration of the group, to give a small table showing the relations between the different members :—



We must now proceed to trace out the various changes by which the several substances are obtained.

2. *Methyl-heptenone.*

As can be seen from the foregoing table, the substance from which all the other members of the citral group are built up is the ketone methyl-heptenone. We have already encountered this compound among the decomposition products of cineolic acid, but in that place we did not deal with its constitution.

Methyl-heptenone has been synthesized in different ways by Barbier and Bouveault,[1] Verley,[2] Tiemann,[3] Leser,[4] and Ipatjew.[5] We need only give one synthesis here, and may choose that of Barbier and Bouveault. In the first place, 2-methyl-2, 4-dibromobutane is condensed with the sodium derivative of acetylacetone. This gives the unsaturated diketone (II.), which can be broken down by strong alkali into acetic acid and methyl-heptenone (III.)—

---

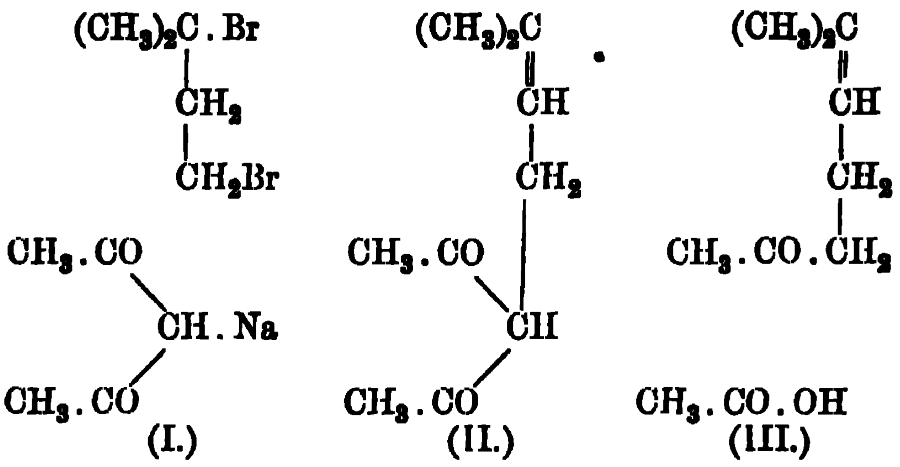
[1] Barbier and Bouveault, *C. R.*, 1896, **122**, 393.

[2] Verley, *Bull. soc. chim.*, 1897, [iii.], **17**, 180.

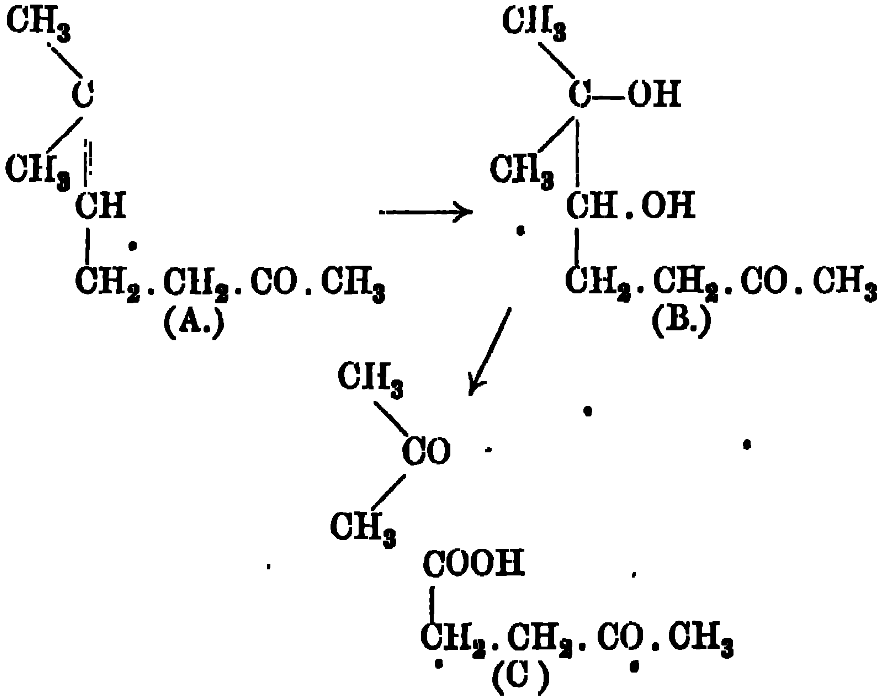
[3] Tiemann, *Ber.*, 1898, **31**, 824.

[4] Leser, *Bull. soc. chim.*, 1897, [iii.], **17**, 180.

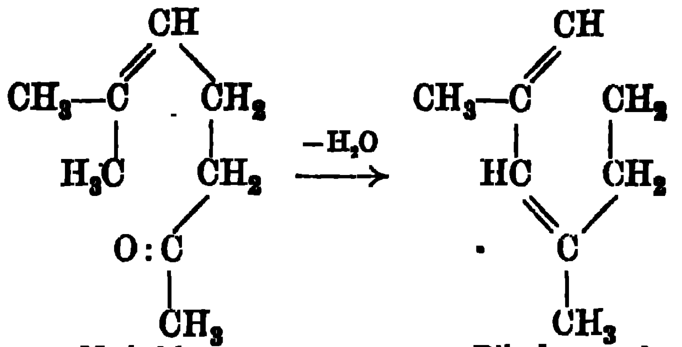
[5] Ipatjew, *Ber.*, 1901, **34**, 594.



This establishes the constitution of the substance, but if further proof were required it is to be found in the behaviour of methyl-heptenone (A) on oxidation. The first product (B) is a dihydroxy-ketone, which, on further oxidation, breaks down into acetone and lævulinic acid (C)—



In itself, methyl-heptenone is of no great importance, and we may confine ourselves to one of the reactions which it undergoes. When shaken with 75 per cent. sulphuric acid it loses a molecule of water and is converted into dihydro-*m*-xylene—

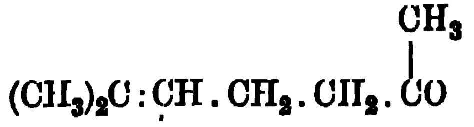


Methyl-heptenone. Dihydro-*m*-xylene.

3. *Geranic Acid.*

Following upon their synthesis of methyl-heptenone, Barbier and Bouveault[1] were enabled to synthesize geranic acid by means of a simple series of reactions. By the action of zinc and iodo-acetic ester upon methyl-heptenone they prepared a hydroxy-acid, which, on boiling with acetic anhydride, broke down into geranic acid.

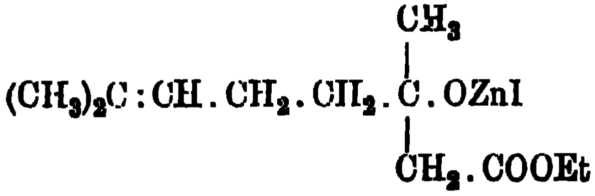
The formulæ below indicate the course of the synthesis—



$$(CH_3)_2C:CH.CH_2.CH_2.\overset{\overset{\displaystyle CH_3}{|}}{C}O$$

Methyl-heptenone.

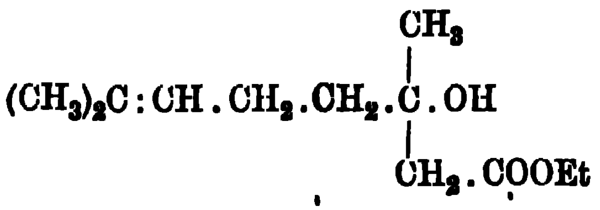
Zinc and iodoacetic ester.



$$(CH_3)_2C:CH.CH_2.CH_2.\underset{\underset{\displaystyle CH_2.COOEt}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}.OZnI$$

Intermediate product.

Water.



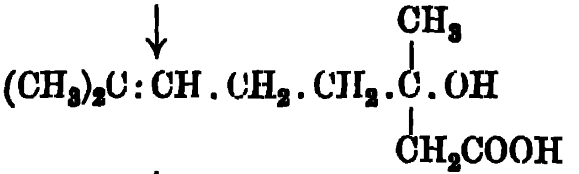
$$(CH_3)_2C:CH.CH_2.CH_2.\underset{\underset{\displaystyle CH_2.COOEt}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}.OH$$

Hydroxydihydrogeranic ester.

Hydrolysis.

---

[1] Barbier and Bouveault, *Compt. rend.*, 1896, 122, 398; see also Tiemann, *Ber.*, 1898, 31, 825.

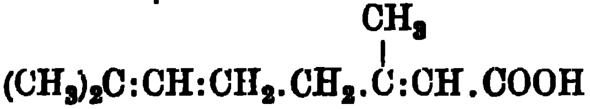


$$\downarrow$$

$$(CH_3)_2C:CH.CH_2.CH_2.\overset{CH_3}{\underset{CH_2COOH}{C}}.OH$$

Hydroxydihydrogeranic acid.

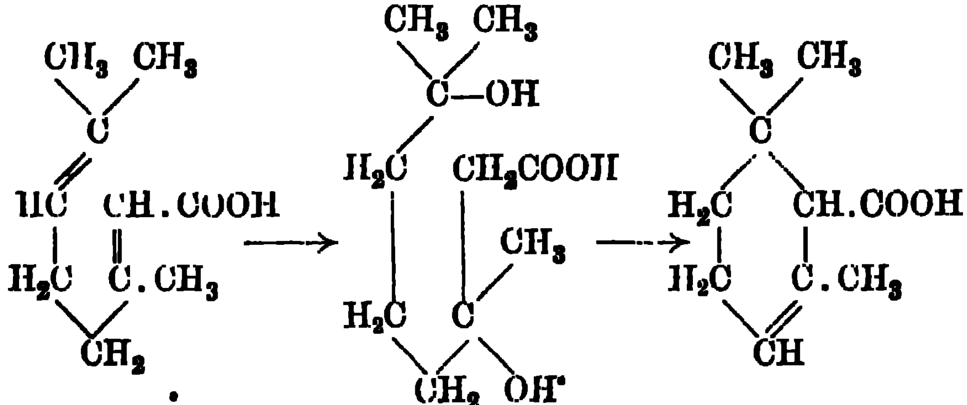
↓ *Dehydration with acetic anhydride.*



$$(CH_3)_2C:CH:CH_2.CH_2.\overset{CH_3}{C}:CH.COOH$$

Geranic acid.

Like methyl-heptenone, geranic acid is of very little importance in itself. The only reaction which specially concerns us is its condensation to *a*-cyclogeranic acid,[1] which, like the corresponding condensation of methyl-heptenone, takes place under the influence of 70 per cent. sulphuric acid. In order to explain the geranic acid change, it is necessary to assume the formation and decomposition of an intermediate product which has not yet been isolated—



Geranic acid. Hypothetical intermediate product. *a*-Cyclogeranic acid.

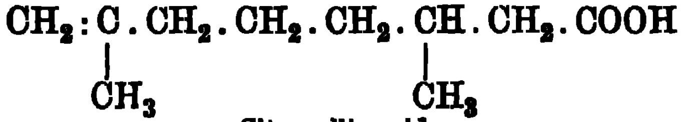
As the table shows, geranic acid gives rise to two series of compounds: on the one hand, by reduction, we may obtain rhodinic acid and its derivatives; while on the other we may produce the aldehyde citral, from which in turn several substances may be formed. In the first place, we may deal with the smaller group, rhodinic acid and its allied compounds.

4. *Rhodinic Acid, Rhodinol, and Rhodinal.*

When the ethyl ester of geranic acid is reduced by means of sodium and amyl alcohol it is converted into inactive rhodinic acid.[1] The active, lævo-rotatory form of this acid has been obtained from the active alcohol rhodinol. These two acids are isomeric with citronellic acid, which is obtained by the oxidation of the aldehyde citronellal, and it has been suggested that citronellic acid is the dextro-form of rhodinic acid. On the other hand, from the constitution of citronellal, we should expect that citronellic acid obtained from it by oxidation would have the formula (I.), while rhodinic acid from geranic acid should have the formula (II.).

---

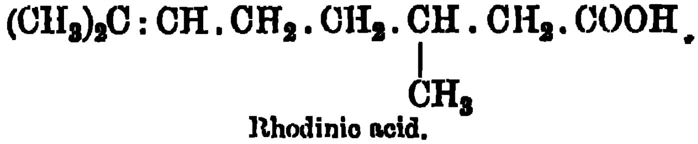
[1] Tiemann and Semmler, *Ber.*, 1893, 26, 2726: Tiemann and Schmidt, *ibid.*, 1898, 31, 881; Tiemann and Tigges, *ibid.*, 1900, 33, 3713; Barbier and Bouveault, *Bull. soc. chim.*, 1896, [iii.], 15, 1002.



$$CH_2 : \underset{\displaystyle CH_3}{\underset{|}{C}} . CH_2 . CH_2 . CH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . CH_2 . COOH$$

Citronellic acid.

(I.)



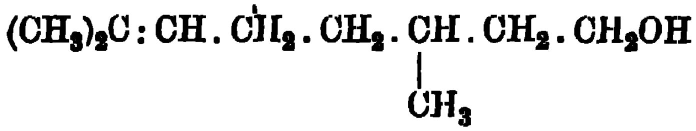
$$(CH_3)_2C : CH . CH_2 . CH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . CH_2 . COOH$$

Rhodinic acid.

(II.)

The literature of the subject is somewhat contradictory, and it does not seem necessary to go into the question in detail here.

When the ester of rhodinic acid is reduced by means of sodium and absolute alcohol it yields the corresponding alcohol[2] rhodinol—



$$(CH_3)_2C : CH . CH_2 . CH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . CH_2 . CH_2OH$$

which is isomeric with citronellol. Here, again, the literature is contradictory, and it seems impossible to decide whether the two compounds are stereo-isomers or differ in structure.

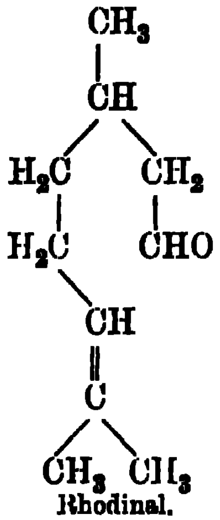
Rhodinal,[3] the aldehyde corresponding to the alcohol rhodinol, is obtained by distilling together calcium formate and the calcium salt of rhodinic acid. Barbier and Bouveault regard it as having the structure (I.), because of its conversion into menthone. Citronellal, with which it is isomeric, when submitted to the action of acetic anhydride, is changed into isopulegol, as we have already described. On the other hand, rhodinal when treated in the same way yields menthone—

---

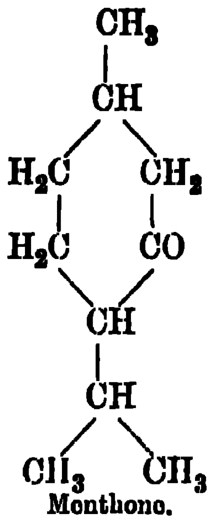
[1] Tiemann, *Ber.*, 1898, 31, 2901.

[2] Bouveault and Gourmand, *Compt. rend.*, 1904, 138, 1699.

[3] Tiemann, *Ber.*, 1898, 31, 2902.



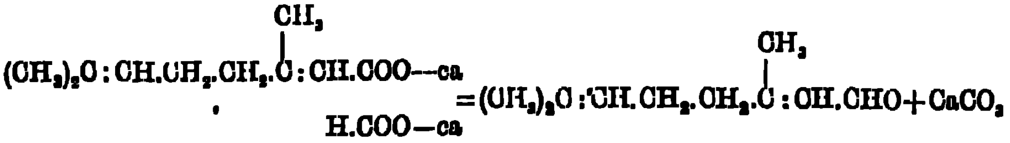
Rhodinal.
(I.)



Menthone.
(II.)

5. *Citral.*

By distilling together the calcium salts of formic and geranic acids we obtain the aldehyde citral.[1] Since this is a general reaction, the constitution of citral would probably be that shown in the equation below—



$$\begin{array}{l}(CH_3)_2C:CH.CH_2.CH_2.\overset{CH_3}{\overset{|}{C}}:CH.COO-ca \\ \qquad\qquad\qquad\qquad H.COO-ca\end{array} = (CH_3)_2C:CH.CH_2.CH_2.\overset{CH_3}{\overset{|}{C}}:CH.CHO+CaCO_3$$

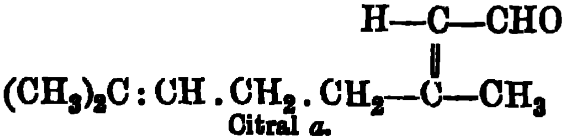
In support of this formula we may quote the decomposition of citral into acetaldehyde and methyl-heptenone, which takes place when the substance is warmed with a solution of sodium carbonate.

Citral, therefore, represents rhodinal or citronellal from which two hydrogen atoms have been withdrawn; and differs from them further in that it contains no asymmetric carbon atom. But though it loses this possibility of isomerism, it retains another, for it has been found to occur in two geometrically isomeric forms[2]—

---

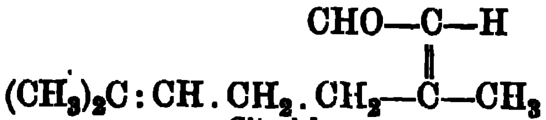
[1] Tiemann, *Ber.*, 1898, **31**, 827, 2899.

[2] *Ibid.*, 1899, **32**, 115; 1900, **33**, 877; Bouveault, *Bull. soc. chim.*, 1899, [iii.], **21**, 419, 423; Barbier, *ibid.*, 635; Kerschbaum, *Ber.*, 1900, **33**, 886; Zeitschel, *Ber.*, 1906, **39**, 1783; Harries and Himmelmann, *Ber.*, 1907, **40**, 2823.



$$(CH_3)_2C:CH.CH_2.CH_2-\overset{\overset{\text{H—C—CHO}}{\|}}{C}-CH_3$$

Citral *a*.

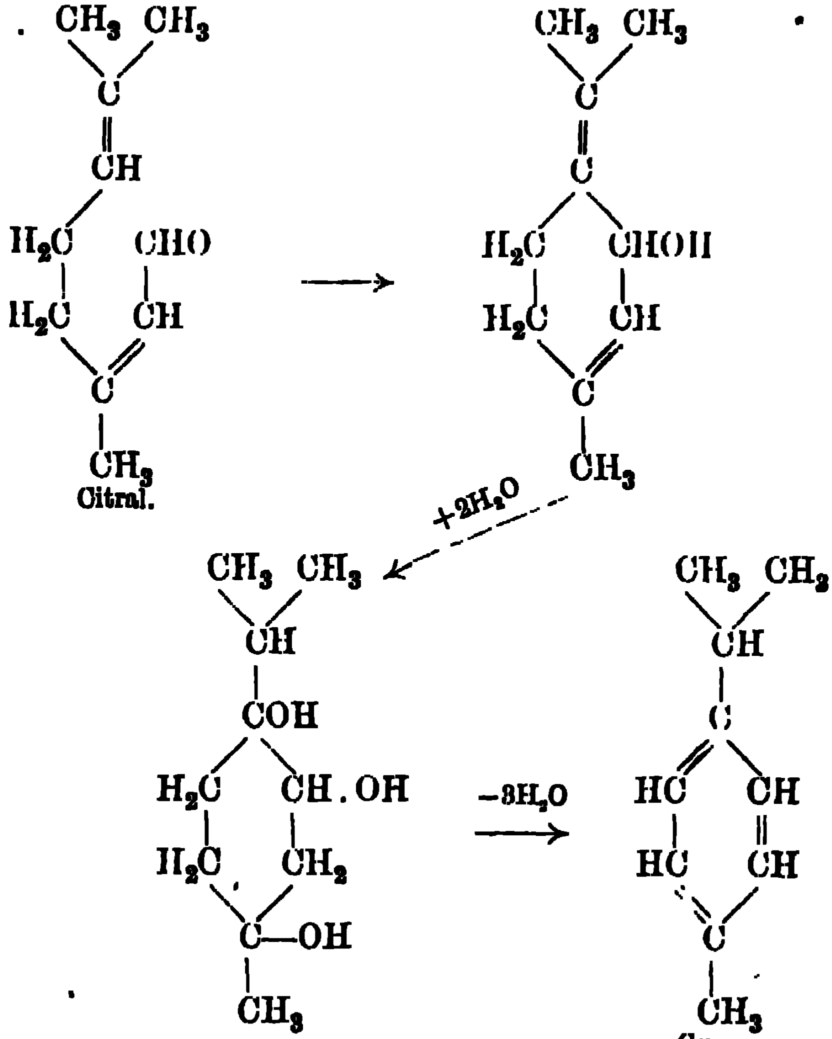


$$(CH_3)_2C:CH.CH_2.CH_2-\overset{\overset{\text{CHO—C—H}}{\|}}{C}-CH_3$$

Citral *b*.

These have been shown by Harries and Himmelmann to be structurally identical; and the relative configurations have been deduced from the relations of the two compounds to geraniol and nerol, with which we shall deal later.

Like the other olefinic terpenes, citral can be converted into cyclic substances with great ease. When it is boiled for a long time with glacial acetic acid it is changed into cymene [1]—



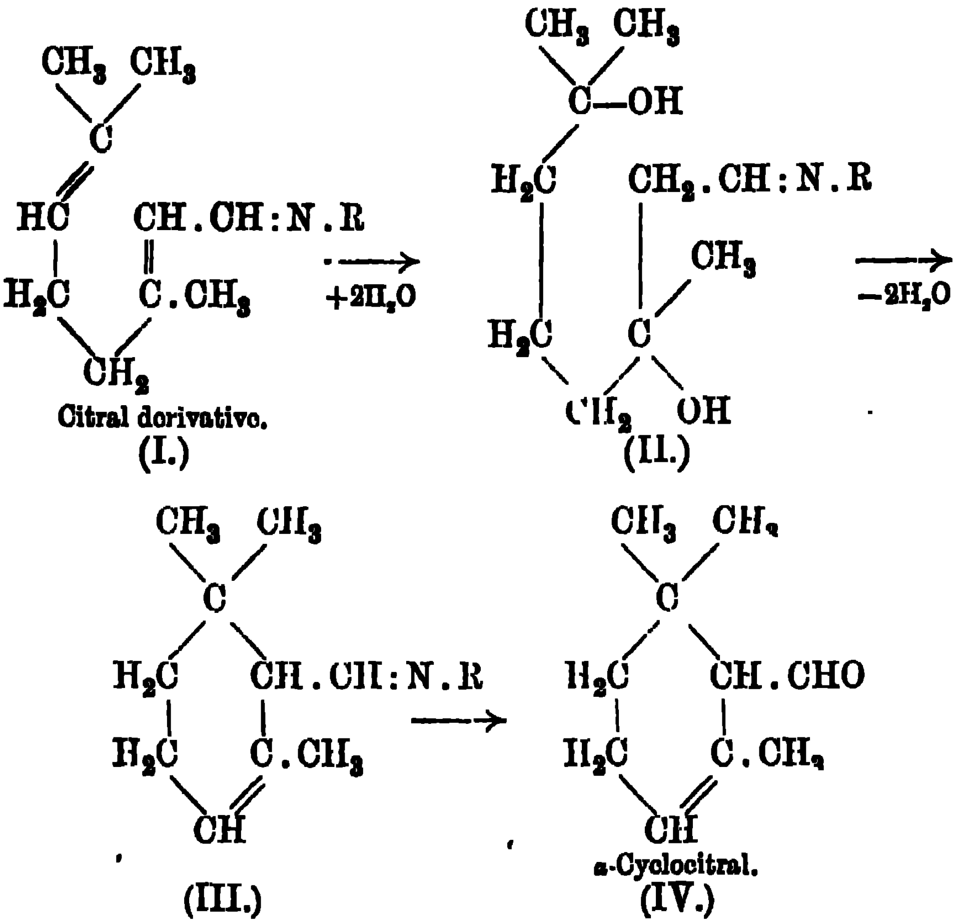
Citral.

Cymene.

---

[1] Tiemann and Semmler, *Ber.*, 1895, **28**, 2134.

A second condensation of citral takes place when the aldehyde group is so treated that it takes no part in the action. For instance, if we condense citral with a primary amine, we obtain a cyclo-citral by a simple wandering of bonds and ring-formation—



The same result may be obtained by condensing citral with cyan-acetic ester instead of an amine. In each case, the amine or cyan-ester can be split off after the condensation to cyclocitral has taken place.

Cyclo-citral occurs in two isomeric forms,[1] the formation of either being dependent upon the manner in which water is eliminated from the molecule of an intermediate hydration product (II.). The formation of β-cyclocitral takes place as shown below—

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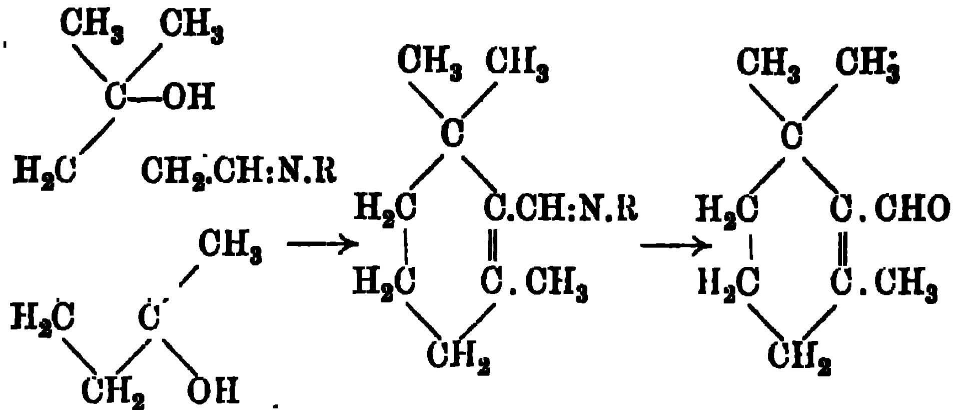
[1] Tiemann, *Ber.*, 1900, 33, 3719.

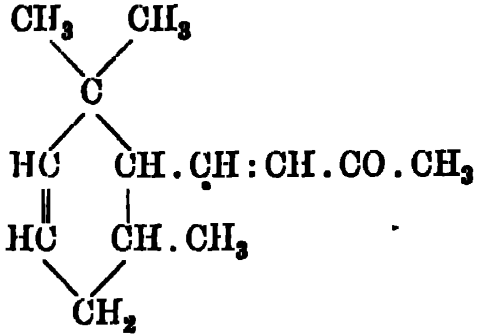


(II.)

β-Cyclocitral.

The practical interest of citral lies in the fact that when it is condensed with acetone by means of baryta, it yields a substance, pseudo-ionone, which, by the action of sulphuric acid, is changed into ionone,[1] the basis of artificial violet perfume (see formulæ, p. 98).

This body differs from the natural substance irone (to which the odour of violets is due) only in the position of a double bond—



Irone.

6. *Geraniol, Nerol, and Linalool.*

If we reduce citral with sodium amalgam in an alcoholic solution weakly acidified with acetic acid, a mixture of two isomeric alcohols, geraniol and nerol, is obtained. These two bodies, on oxidation, regenerate citral, and on this ground, as well as on account of other reactions common to both, it is

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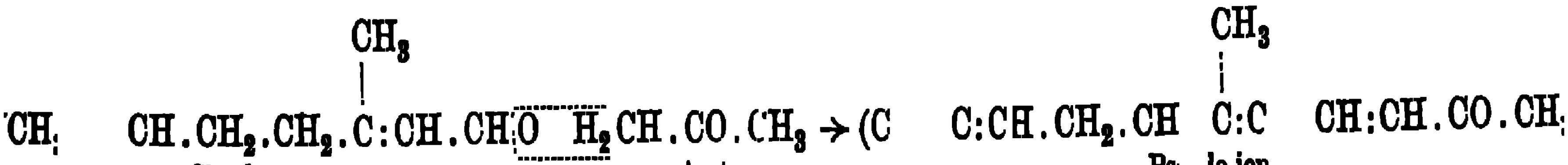
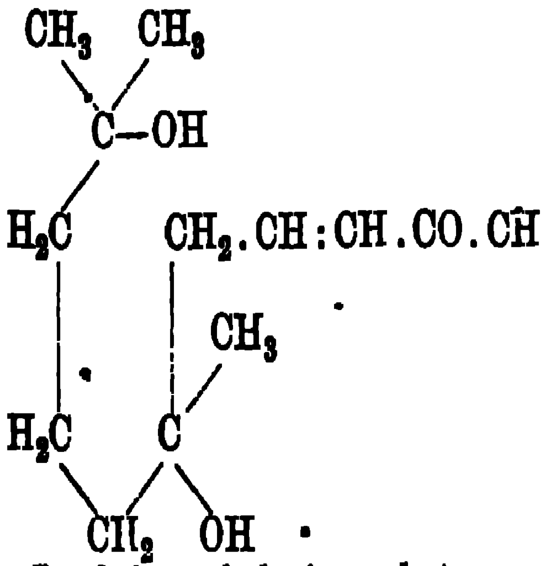
[1] Tiemann and Krüger, *Ber.*, 1893, 26, 2691; Tiemann, *ibid.*, 1898, 31, 808, 867, 1736, 2318; 1899, 32, 827; Tiemann and Schmidt, *ibid.*, 1900, 33, 3708.

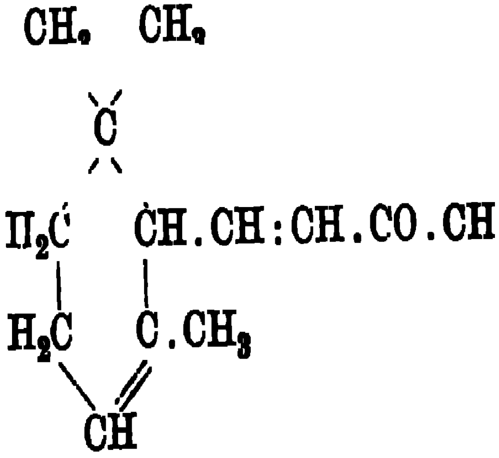


$CH \quad CH.CH_2.CH_2.\overset{\overset{CH_3}{|}}{C}:CH.CH\boxed{O \quad H_2}CH.CO.CH_3 \rightarrow (C \quad C:CH.CH_2.CH \quad \overset{\overset{CH_3}{|}}{C}:C \quad CH:CH.CO.CH$

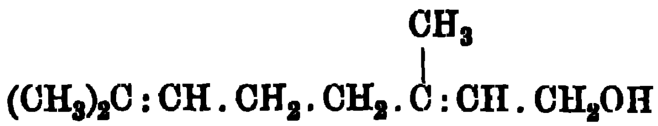
Citral. Acetone. Ps lo-ion



Pseudo-ionone hydration product.



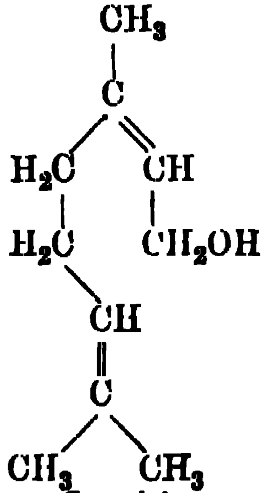
assumed that they are structurally identical but stereoisomeric substances of the formula—



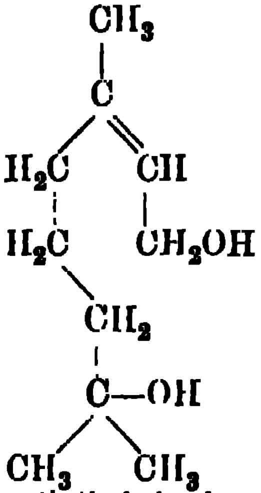
$$(CH_3)_2C:CH.CH_2.CH_2.\overset{\overset{\displaystyle CH_3}{|}}{C}:CH.CH_2OH$$

Proof of the correctness of this formula is afforded by the fact that when geraniol is heated with water to 150° C. it gives ethyl alcohol and methyl-heptenone; while on oxidation it gives acetone, lævulinic acid, and oxalic acid.

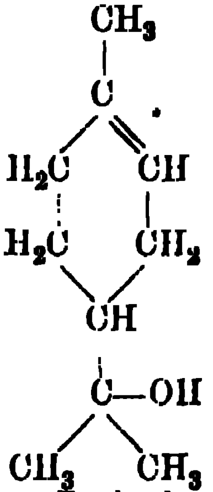
By the action of acetic acid, to which 1 or 2 per cent. of sulphuric acid has been added, both nerol and geraniol give terpineol—



Geraniol.

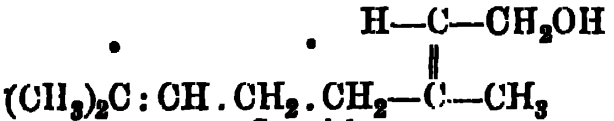


Hypothetical glycol.



Terpineol.

Now, this reaction takes place nine times faster with nerol than with geraniol; and if the two bodies are geometrical isomers, this difference allows us to draw a conclusion with regard to their configurations.[1] A comparison of the two formulæ below will suffice to show that in (I.) the groups which unite to form the terpineol ring are further apart in space than they are in (II.). The ring-formation will therefore occur more easily in the case of (II.) than in that of (I.). Hence we must ascribe to geraniol the first formula, and to nerol the second—



$$(CH_3)_2C:CH.CH_2.CH_2-\overset{\overset{\displaystyle H-C-CH_2OH}{\|}}{C}-CH_3$$

Geraniol.

(I.)

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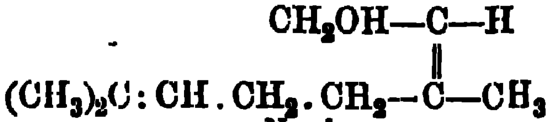
[1] Zeitschel, *Ber.*, 1906, **39**, 1780.

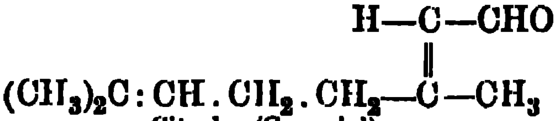


$$\begin{array}{rcl} \mathrm{CH_2OH-} & \mathrm{C} & \mathrm{-H} \\ & \| & \\ \mathrm{(CH_3)_2C:CH.CH_2.CH_2-} & \mathrm{C} & \mathrm{-CH_3} \end{array}$$

Nerol.

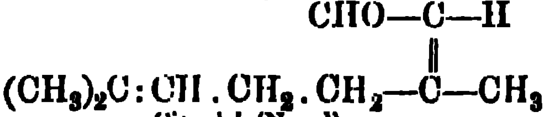
(II.)

We are now able to deal with the space formulæ of the two citrals. The oxidation of geraniol gives a mixture of citral *a* and citral *b*, in which citral *a* predominates; while with nerol the proportions are reversed, more citral *b* being formed. From this we may deduce that citral *a* has the same configuration as geraniol, while citral *b* has its groups arranged as in nerol—



$$\begin{array}{rcl} \mathrm{H-} & \mathrm{C} & \mathrm{-CHO} \\ & \| & \\ \mathrm{(CH_3)_2C:CH.CH_2.CH_2-} & \mathrm{C} & \mathrm{-CH_3} \end{array}$$

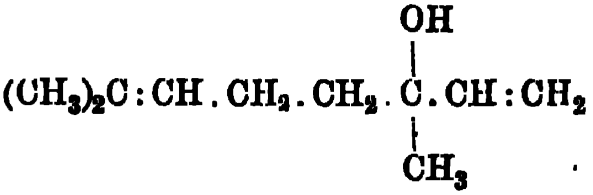
Citral *a* (Geranial).



$$\begin{array}{rcl} \mathrm{CHO-} & \mathrm{C} & \mathrm{-H} \\ & \| & \\ \mathrm{(CH_3)_2C:CH.CH_2.CH_2-} & \mathrm{C} & \mathrm{-CH_3} \end{array}$$

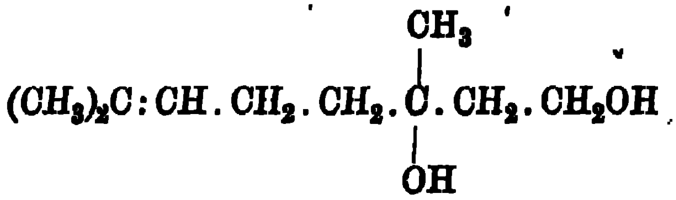
Citral *b* (Neral).

Both geraniol and nerol are found in nature as inactive substances, which agrees with the formulæ which we have ascribed to them above. The isomeric compound, linalool, however, occurs in both dextro- and lævo-rotatory forms, and must therefore contain an asymmetric carbon atom. The inactive form of linalool is convertible into both geraniol and nerol by the action of acetic anhydride. This reaction can be explained by assuming that linalool has the formula—



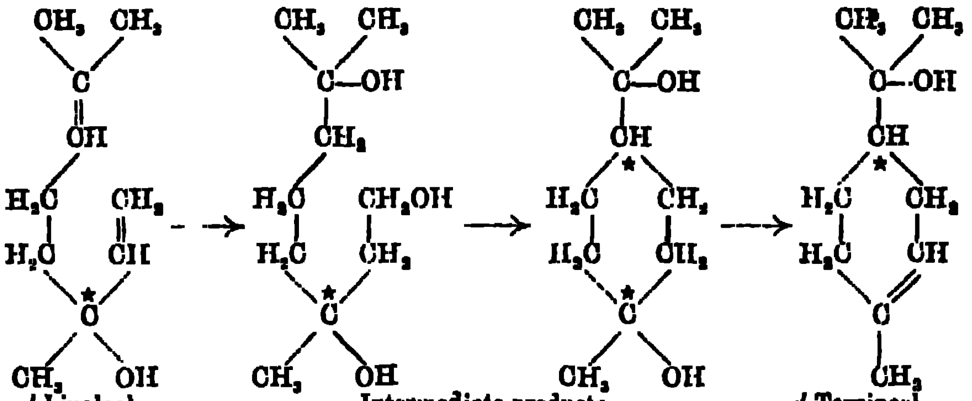
$$\begin{array}{rcl} & \mathrm{OH} & \\ & | & \\ \mathrm{(CH_3)_2C:CH.CH_2.CH_2.} & \mathrm{C} & \mathrm{.CH:CH_2} \\ & | & \\ & \mathrm{CH_3} & \end{array}$$

A comparison of the formulæ of geraniol, nerol, and this one proposed for linalool will show that by the addition of water to each of these substances we can produce in all three cases the same glycol of the formula—



$$\begin{array}{rcl} & \mathrm{CH_3} & \\ & | & \\ \mathrm{(CH_3)_2C:CH.CH_2.CH_2.} & \mathrm{C} & \mathrm{.CH_2.CH_2OH} \\ & | & \\ & \mathrm{OH} & \end{array}$$

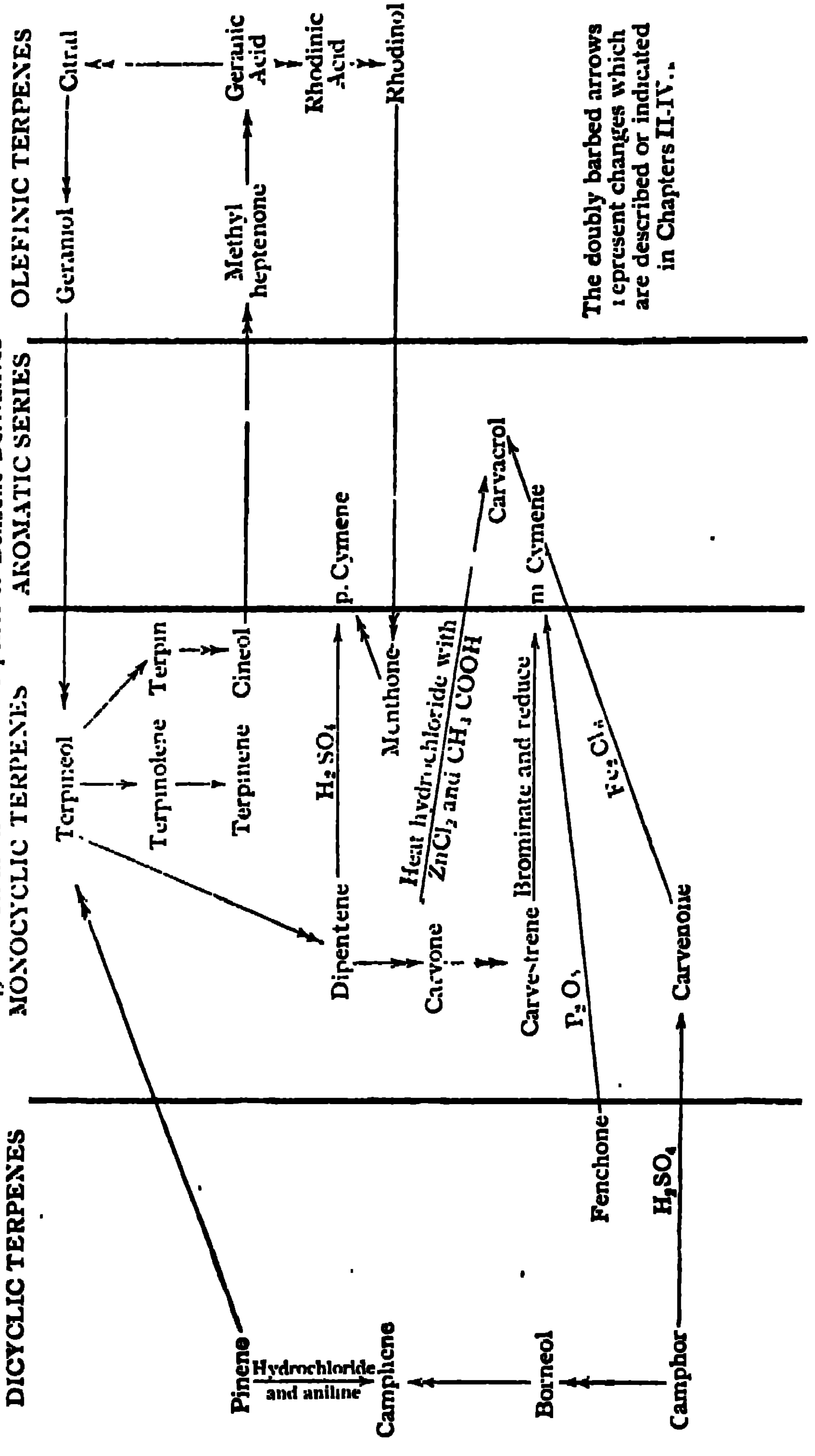
This formation of a common hydration product suffices to explain the interconvertibility of the three isomers; but there is one point which seems to render the linalool formula rather doubtful. When we take lævo-linalool and treat it with acetic anhydride, terpineol is formed along with nerol and geraniol; and this terpineol is found to be dextro-rotatory. But when we compare the formulæ of terpineol and linalool, we find that the asymmetric carbon atom of linalool does not correspond to that in terpineol; in fact, the atom which in linalool was asymmetric is now not asymmetric, while a new asymmetric carbon atom has come into being. How optical activity can persist through such a change as this appears difficult to understand, unless we assume that it is a case of asymmetric synthesis.



l-Linalool. Intermediate products. *d*-Terpineol.

This terminates our survey of the terpene class. In conclusion, we may append to this chapter a table showing some of the possible conversions of mono-cyclic, di-cyclic, and olefinic terpenes into each other, and also into members of the benzene series.

Table showing some Relations between Terpenes & Benzene Derivatives



The doubly barbed arrows represent changes which are described or indicated in Chapters II-IV.

CHAPTER V

RUBBER

1. INTRODUCTORY.

THE exact distribution of credit among the pioneers in the chemistry of rubber has in recent years produced a most unedifying amount of controversy;[1] and insinuations have been made by at least one German chemist which appear to overstep the bounds of normal scientific polemics. In these circumstances, it seems desirable to give an outline of the history of the subject in its earlier stages.

In 1860 Williams[2] observed that when rubber is distilled it yields what are now known as isoprene and dipentene. On leaving isoprene in a partly-filled bottle for some months, he noticed that it became oxidized and was converted into a viscid liquid. When this viscid material was distilled, at one point in the process the liquid solidified to "a pure white spongy elastic mass" which, when burned, gave off the characteristic odour of burning rubber. The material in question, on analysis, yielded the following results: 78·8 per cent. carbon, 10·7 per cent. hydrogen, and 10·5 per cent. oxygen. This composition corresponds to isoprene plus half a molecule of oxygen.

Bouchardat[3] in 1879 found that when hydrochloric acid solution is allowed to act upon isoprene, one of the products, after the reaction has proceeded for a fortnight or three weeks, is a non-volatile body having the composition $C = 87{\cdot}1$ per cent., $H = 11{\cdot}7$ per cent., and $Cl = 1{\cdot}7$ per cent. If the chlorine be disregarded—and Bouchardat believed that its presence was due to contamination by foreign chlorinated compounds—these results agree closely with the formula $(C_5H_8)_x$. The substance thus produced "possesses the elasticity and other characteristics of rubber. It is insoluble in alcohol; it swells up in ether, also in carbon disulphide in which it dissolves in the manner of natural rubber." When submitted to dry distillation "it forms the same volatile hydrocarbons as rubber." "All these properties appear to identify this polymer of isoprene with the substance from which isoprene is formed, namely rubber."

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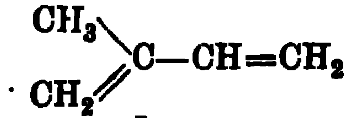
[1] For a complete account of this see Pond, *J. Amer. Chem. Soc.*, 1914, **36**, 165. See also Luff, *J. Soc. Chem. Ind.*, 1916, **35**, 983.

[2] Williams, *Phil. Trans.*, 1860, 245; *Proc. Roy. Soc.*, **10**, 516.

[3] Bouchardat, *Compt. rend.*, 1879, **89**, 1117.

Harries[1] has in recent times criticized this work of Bouchardat and has attempted to prove that Bouchardat's method does not yield the products described. Unfortunately for his contentions, he had read the original paper so carelessly that he apparently attempted a repetition of the work by the employment of hydrochloric acid *gas* whereas Bouchardat used aqueous hydrochloric acid. When an attempt is made to repeat an author's work it is usual to employ his own method; not to try a new one and then declare that the described method "seems almost excluded." Harries also[2] asserted that Bouchardat had not proved the identity of his product with true rubber. It is difficult to see what more Bouchardat could have done, considering the date at which he worked; and this attitude in the critic becomes more astonishing when it is recalled that in 1910–11 Harries made use of tetrabromides, nitrosites, and ozonides as tests to distinguish rubber; but in 1912–13 he discarded these as being inefficient, and concentrated his attention upon the rate of decomposition of the ozonides with water.[3]

The next stage in the history of synthetic rubber is marked by Tilden's paper of 1882.[4] Tilden showed that when turpentine vapour is passed through a red-hot tube, isoprene—



$$\begin{matrix}CH_3\diagdown & \\ & C-CH=CH_2 \\ CH_2\diagup\!\!\diagup & \end{matrix}$$

Isoprene.

is formed; and he also stated that, by the action of nitrosyl chloride, isoprene was converted into rubber. Ten years later, Tilden[1] made public the fact that some isoprene which had been kept in a bottle for a long time had undergone change. "In place of the limpid colourless liquid the bottles contained a dense syrup in which were floating several large masses of solid, of a yellowish colour. Upon examination this turned out to be indiarubber." These original samples have now been tested by the ozone method and were found to be true rubber.[2] It may be noted that this work of Tilden's should be regarded as a real synthesis of rubber, and stands in a different category from Bouchardat's. Bouchardat obtained his isoprene by distilling rubber; so that his work consisted of *re-synthesizing* rubber from its decomposition products. Tilden, on the other hand, obtained his isoprene from turpentine, and may thus claim to have made a true synthesis of rubber.

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[1] Harries, *Annalen*, 1913, **395**, 211.

[2] *Ibid.*, *Gummi-Zeitung*, 1910, **24**, 853.

[3] *Ibid.*, Lecture at Vienna, 12th March, 1910; *Chem. Zeit.*, 1910, **34**, 316; *Annalen*, 1913, **395**, 211.

[4] Tilden, *Chem. News*, 1882, **46**, 220.

Harries,[3] not having been able to repeat Tilden's work, contented himself with the statement that Tilden "never proved that he had rubber in his hands."

About 1899 or 1900, Kondakoff[4] showed that other members of the isoprene series could be converted into rubber-like materials by various methods.

In the earlier part of the present century, the uses of rubber were greatly extended; and as a natural consequence there was a marked effort to produce the material by artificial means on a manufacturing scale.

In 1909 Hofmann[5] discovered that isoprene may be converted into rubber by the action of heat. This is claimed as the first technical method of rubber synthesis. If it be a practical method it appears curious that, during the war, many reports were current crediting Germany with smuggling rubber in from America *viâ* parcel post.

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[1] Tilden, Paper read before the Philosophical Society of Birmingham, 1892.

[2] *Ibid.*, *Chemical Discovery and Invention in the Twentieth Century*, 1916; Pickles, *Trans.*, 1910, 97, 1085.

[3] Harries, Vienna Lecture, 1910.

[4] Kondakoff, *On Synthetic Rubber* (in Russian) (1912); *J. pr. Chem.*, 1900, **62**, 175; 1901, **63**, 113; **64**, 109. See also Harries' Vienna Lecture and *Annalen*, 1911, **383**, 180.

[5] See Duisberg, *Eighth International Congress of Applied Chemistry*, 1912, **28**, 50, 86.

In 1908 a British syndicate quietly set to work upon the problem of the commercial synthesis of rubber.[1] A method of obtaining isoprene from fusel oil was worked out, thereby ensuring that the raw material should not be too expensive. In the course of some experiments, it occurred to Matthews to study the influence of sodium upon isoprene; and in July, 1910, he sealed the two substances up in a tube. Inspection of the tube in August showed that the contents had become viscid and contained a proportion of remarkably good rubber. The vessel was resealed and left till September, when it was found to contain a solid mass of amber-coloured rubber. A patent was applied for on 25th October, 1910.

Meanwhile Harries, the Badische Anilin und Soda Fabrik and Bayer and Co. were also at work, and the race was becoming a close one. Harries' story is as follows.[2] He claims that in February, 1910, he observed, during a purification of isoprene by distilling it over sodium, that the metal had an "altering" (veränderende) action upon the hydrocarbon. The fact that rubber-like materials resulted from the process was first established "in September or October," which is rather vague. He states that on 28th October, 1910, he verbally communicated his discovery to a representative of the Elberfeld Farbenfabriken in Berlin, and suggested that a patent should be taken out by them. This patent was applied for in Germany on 12th December, 1910, seven weeks after the British syndicate had applied for their English patent.

If we were to apply to Harries' story the same rigid scrutiny as he spent upon the work of Bouchardat and Tilden, the only evidence which we could regard as relevant would be the actual date of the patent application, as no corroboration has been offered by the other details.* In any case, under modern conditions, priority of discovery counts for less than priority of publication; and on that basis the Germans lost the race.

The controversy which arose out of this defeat was marked by especial bitterness on the part of Harries;[1] and it is a matter for congratulation that chemical polemics are not usually conducted in that spirit. When a person devotes many pages to an attempt to demonstrate that German chemists have a prior claim to a subject, it seems peculiar to find him complaining against "the dragging in of nationalistic motives in scientific work." Before the war threw a flood of light upon German psychology, we should have been somewhat at a loss to comprehend this mental attitude.

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[1] See Perkin, *J. Soc. Chem. Ind.*, 1912, **31**, 616.

[2] Harries, *Annalen*, 1912, **395**, 211.

* The first scientific publication by Harries on the subject is dated 26th June, 1911 (*Annalen*, **383**, 188), and he there states (before the controversy arose) that he made the discovery at the *end* of 1910 (Ende des Jahres 1910).

2. THE PROPERTIES AND CONSTITUTION OF NATURAL RUBBER.

Natural rubber or caoutchouc is a transparent, tough elastic substance having no definite melting- or boiling-point.[*] It absorbs water, increasing in volume as it does so. It is soluble in several organic liquids, such as benzene, chloroform, carbon tetrachloride, dipentene, ligroin, and carbon disulphide. Its composition corresponds to the formula $(C_5H_8)_x$. It is unsaturated, combining readily with oxygen and chlorine; and it yields nitrosites and nitrosates with nitrous fumes. When distilled, it breaks down into a mixture of hydrocarbons of which the chief are isoprene and dipentene. When heated with sulphur or when treated with solutions of sulphur dichloride in carbon disulphide, it becomes "vulcanized," the process resulting in the rubber retaining its elastic properties over a wider range of temperature than when raw. When a high percentage of sulphur is introduced, vulcanite is produced.

Apart from the actions of halogens and nitrous fumes upon rubber, which have led to little, our knowledge of its constitution depends upon its behaviour with ozone.

Harries[2] states that when rubber is treated with ozone and the resulting ozonide is decomposed with water, the only isolable products are lævulinic aldehyde, lævulinic acid, and the peroxide of lævulinic aldehyde. The acid is evidently a secondary product of reaction.

The molecular weight of the ozonide shows that its composition is $C_{10}H_{16}O_6$, which points to the fact that the structure from which it was derived must have contained two double bonds, each of which has taken up one molecule of ozone.

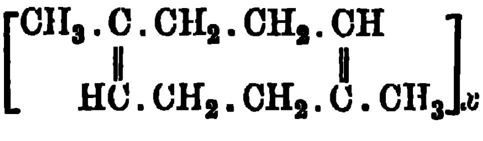
---

[1] Harries, *Annalen*, 1912, **395**, 211.

[*] It appears from some work of Harries that natural Para rubber occurs in at least three forms: oily, soluble, and insoluble.

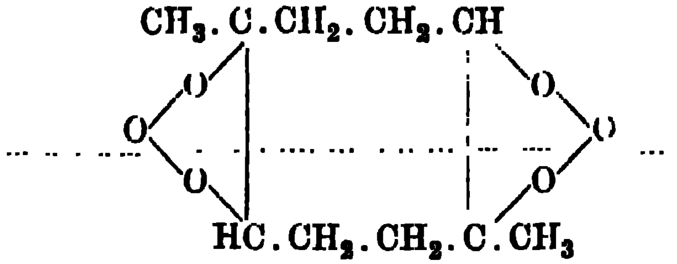
[2] Harries, *Ber.*, 1905, **38**, 1195.

In order to account for these results, Harries has had to resort to an hypothesis which will hardly recommend itself to many chemists. He assumes, from the production of lævulinic aldehyde and its peroxide that rubber has the following structure:—



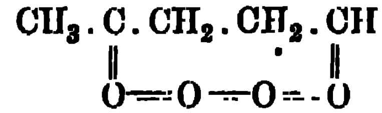
$$\left[\begin{array}{llll} CH_3.C & .CH_2.CH_2. & CH & \\ \quad\ \| & & \ \| & \\ \ \ HC & .CH_2.CH_2. & C & .CH_3 \end{array}\right]_x$$

and that the ozonide has the constitution:



Gives the peroxide.
Gives the aldehyde.

The breakdown of the ozonide is supposed to take place along the dotted line, the lower half of the molecule producing lævulinic aldehyde, $CH_3.CO.CH_2.CH_2.CHO$, whilst the upper half yields the peroxide:—



$$\begin{array}{lll} CH_3.C & .CH_2.CH_2. & CH \\ \qquad\| & & \ \| \\ \qquad O & =O-O= & O \end{array}$$

But at this point difficulties arise; for how can we suppose that the cyclo-octadiene ring can polymerize without destroying the double bonds in it? And if it does polymerize through the agency of the double bonds, how can they be left unchanged to attack the ozone molecules in order to produce the ozonide?

Harries endeavours to gain credence for his hypothesis by adducing the fact that cyclo-octadiene—which should be analogous to his assumed eight-membered ring—does actually polymerize readily; but inadvertently, no doubt, he omits to mention that one of the products of this polymerization is a di-cyclo-octadiene consisting of thin, pointed leaflets of m.p. 114° C.; whilst the other polymer is also a crystalline body.[1]

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[1] Willstätter and Veraguth, *Ber.*, 1905, **38**, 1975.

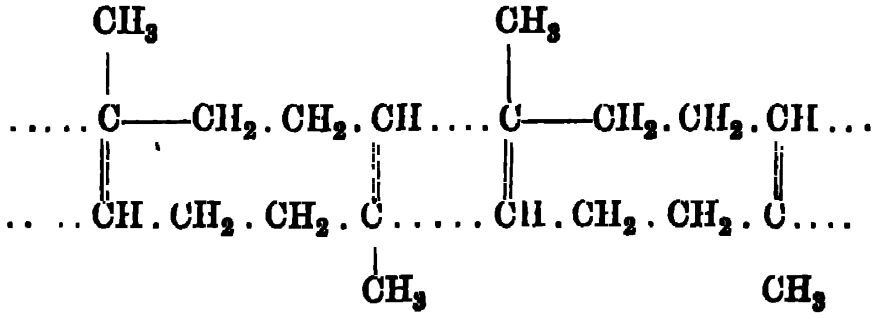
The analogy with the properties of rubber is hardly close enough to support the eight-membered ring theory to any extent worth considering.

For his final demonstration of the presence of an eight-membered ring in the rubber molecule, Harries relied upon the following statements.[1] When the dihydrochloro-derivative of rubber is subjected to the action of pyridine,[2] he found that a substance *different* from rubber is regenerated.* On ozonizing this, he claimed to have isolated a cyclo-octadione derivative among the products. Therefore, according to his argument, the *original* rubber must have contained an eight-membered ring. The fallacy in reasoning is not worth dwelling upon, as it subsequently turned out [3] that he had made a "regrettable error" † and had mistaken an open-chain di-ketone,

$$CH_3 . CO . CH_2 . CH_2 . CH_2 . CO . CH_3$$

for a cyclo-octadione derivative. It seems hardly worth while to comment on the value of such evidence; though Harries still contends that it establishes the presence of an eight-membered ring in the rubber molecule.

Harries [4] proposes to regard the polymerization of the eight-membered rings as a mere kind of loose addition, so that the polymer breaks down into cyclo-octadiene molecules under the influence of ozone. In other words, he regards rubber as being built up from a large number of separate cyclo-octadiene molecules clinging together by means of Thiele's partial valencies, somewhat in the following style:—



$$\begin{array}{l}
\quad\;\; CH_3 \qquad\qquad\qquad\qquad\qquad\qquad CH_3 \\
\quad\;\;\; | \qquad\qquad\qquad\qquad\qquad\qquad\;\;\, | \\
\ldots\ldots C—CH_2 . CH_2 . CH \ldots\ldots C—CH_2 . CH_2 . CH \ldots \\
\quad\;\;\, \| \qquad\qquad\qquad\;\;\, \vdots \qquad\quad\;\; \| \qquad\qquad\qquad\;\;\, \vdots \\
\ldots\ldots CH . CH_2 . CH_2 . C \ldots\ldots CH . CH_2 . CH_2 . C \ldots\ldots \\
\qquad\qquad\qquad\qquad\quad\;\; | \\
\qquad\qquad\qquad\qquad\;\;\; CH_3 \qquad\qquad\qquad\qquad\quad CH_3
\end{array}$$

---

[1] Harries, *Ber.*, 1913, 47, 2590.

[2] *Ibid.*, 733.

* "Dieser (the regenerated substance) ist nicht mehr identisch mit dem natürlichen Kautschuk."

[3] Harries, *Ber.*, 1914, 48, 784.

† "Ein bedauerlicher Irrtum."

[4] Harries, *Ber.*, 1905, 38, 1195, 3985.

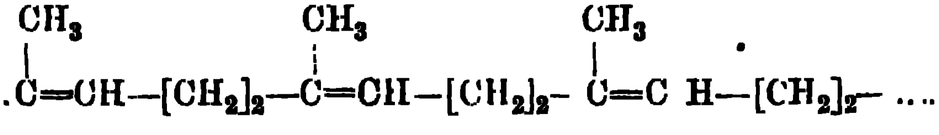
Pickles[1] has adduced several reasons why this conception should not be accepted without further evidence. In the first place, if ozone has the power of depolymerizing this peculiar compound, there seems no reason to deny the same depolymerizing property to other reagents. On this basis, bromine would first break down the colloidal rubber to independent cyclo-octadiene derivatives which would then yield a simple tetrabromo-compound, $C_{10}H_{16}Br_4$; but in actual practice the bromo-derivative of rubber appears to be almost as complex as rubber itself.*

Again, nitrous fumes might be expected to resemble ozone in their effects; but their action on rubber, as studied by Harries himself, produces complicated substance with compositions,† established by molecular weight determinations, corresponding to $C_{20}H_{30}O_{14}N_6$ and even $C_{40}H_{62}O_{24}N_{10}$.

Yet another objection to the physical polymerization idea is to be found in the behaviour of rubber when heated. Under ordinary pressure, heated rubber shows exactly the phenomena ordinarily observed when a complex substance undergoes complete disruption; whilst if the heating be done under reduced pressure, cyclo-octadiene derivatives are not formed, but instead it is found that the simplest compound in the distillate contains at least twenty carbon atoms.‡

This does not exhaust the evidence against Harries' idea; but it is sufficient to indicate some of the weak points of his hypothesis.

Pickles proposes a formula which certainly avoids these difficulties. He suggests that rubber consists of long chains built up from the group C_5H_8 by normal polymerization :—



$$\ldots\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH{-}[CH_2]_2{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH{-}[CH_2]_2{-}\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH{-}[CH_2]_2{-}\ldots$$

The oxidation results require that the two ends of the chain should be linked together; and Pickles assumes that at least eight C_5H_8 complexes are included in a ring. To account for the ozone results, Pickles proposes the hypothesis that after the formation of the ozonide, the linkage between the carbon atoms is ruptured whilst the ozonide chain remains intact till later:—

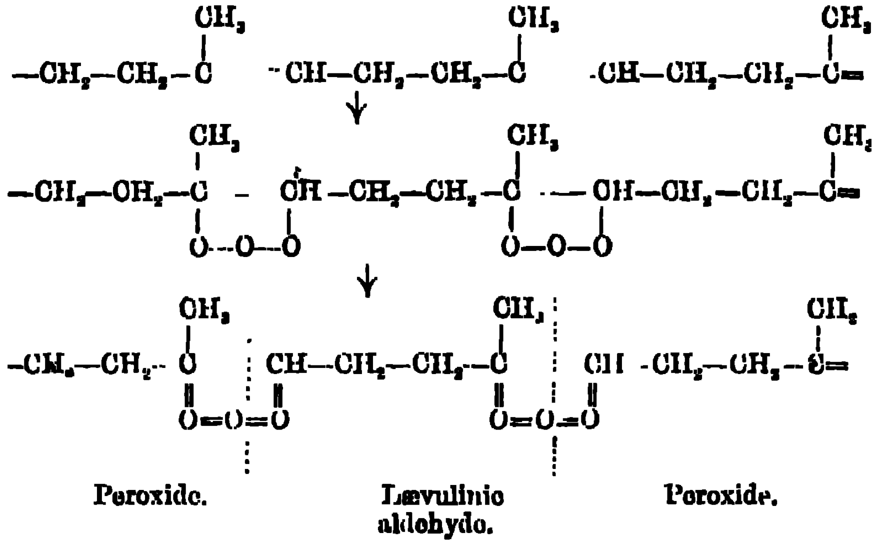
---

[1] Pickles. *Trans.*, 1910, 97, 1085.

* Harries (*Annalen*, 1911, 383, 227) endeavours to get round this by suggesting that the bromo-derivative is an adsorption compound, an hypothesis for which he adduces no evidence.

† Harries (*ibid.*) asserts, in reply to this, that most terpene nitrosites are bimolecular, which would reduce the rubber nitrosite to $C_{10}H_{15}O_7N_3$, thus making the C_8 ring possible.

‡ Harries makes no reply to this argument.



This proposal certainly throws less strain upon the chemist's credulity than is demanded by Harries' hypothesis; and it appears to be supported by the work of Ostromisslenski.[1]

3. The Anglo-French Synthesis of Artificial Rubber.

In devising a manufacturing process on a large scale, the first point to be considered is the possible supply and price of the raw material involved.[2] A synthesis of rubber on a commercial scale might imply a demand running up to 100,000 tons; and before proceeding further it is necessary to make sure that this demand can be filled without producing a shortage in the raw material.

Turpentine appeared at first sight to be a suitable starting-point; but the imports of that substance into this country in the years previous to 1910 were found to average less than 29,000 tons per annum; so that the additional demand for three times that quantity would disturb the market and cause a rise in price which it would be difficult to estimate. Acetone was also ruled out by the question of cost; since, in order to compete with natural rubber, the artificial substitute must be manufactured at a price not exceeding one shilling per pound.*

---

[1] Ostromisslenski, *J. Russ. Phys. Chem. Soc.*, 1915, **47**, 1932.

[2] For a complete account of the history of the syndicate's work, see Perkin, *J. Soc. Chem. Ind.*, 1912, **31**, 616.

The choice of the syndicate fell upon starch, which was readily obtainable at a low price. An alliance was made with Fernbach, of the Pasteur Institute; and this investigator worked out a fermentation process whereby starch (from maize or potatoes) is convertible into fusel oil by one method and into acetone by another. The fusel oil thus obtained was found to contain an exceptionally high percentage of butyl alcohol.

The next stage in the process consists in treating butyl alcohol with hydrochloric acid gas, whereby it is converted into butyl chloride.

By the action of chlorine, a mixture of dichloro-derivatives is obtained from the butyl chloride; and an apparatus was devised which checked the formation of more highly halogenated compounds. The final product contains a mixture of 1,2-, 1,3- and 1,4- dichlorobutane.

Contrary to what might have been expected, these substances, when passed over heated soda-lime, all give rise to the same product: butadiene: $CH_2 : CH . CH : CH_2$. Apparently intramolecular change takes place in the case of 1,2-dichlorobutane, or its product, under the influence of the soda-lime.

The final stage, conversion of the butadiene into artificial rubber, is carried out by allowing the hydrocarbon to stand in contact with a small quantity of sodium, the length of time required ranging from hours to weeks and being dependent upon temperature conditions.

Another method of obtaining artificial rubber has been suggested by Perkin, starting from amyl alcohol. The alcohol is converted into amyl chloride; the latter is then chlorinated, as in the case of butyl alcohol, producing a series of dichloro-derivatives which, when passed over heated soda-lime, yield isoprene. By treatment with metallic sodium, the isoprene polymerizes to an artificial rubber which is different in constitution from the butadiene rubber.

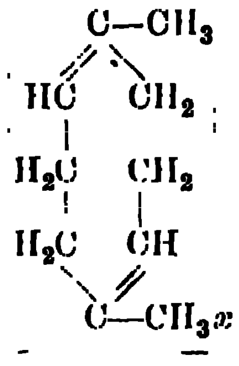
---

* These figures refer, of course, to pre-war prices.

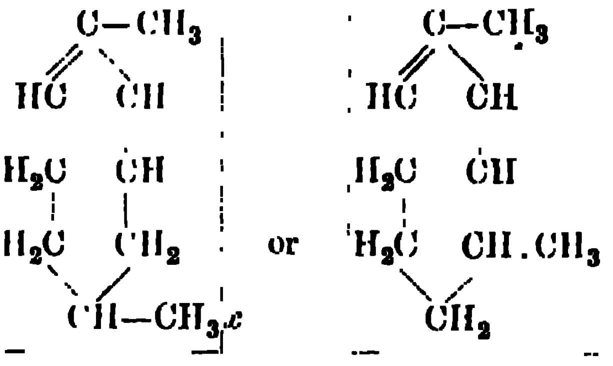
4. Natural Rubber and the Artificial Rubbers.

It must be clearly borne in mind that the synthetic rubbers, though they have many resemblances to natural rubber, are not identical with it in chemical constitution. Some of them, as is evident from their raw materials, are obviously different; whilst even in the case of isoprene polymers we cannot safely assert that their identity with natural rubber is proved.[1]

Harries[2] states that the autopolymerization of isoprene gives rise in the main to what he calls a "normal" product; but that along with this is formed in small yield a different substance. On his ring-hypothesis, the formulæ of these bodies are shown below:—



Normal form.



By-product.

The proof adduced in favour of the by-product structure is that he thinks he isolated methyl-glyoxal among the decomposition products of the ozonide.[3]

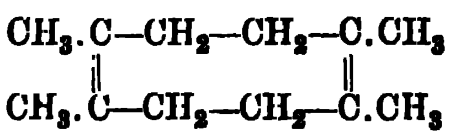
In the case of the polymer of dimethyl-butadiene, two ozonides were obtained which, on decomposition, yielded acetonylacetone and some strong reducing substances. From this Harries deduced that along with the "normal" polymer in this case there must be produced another which yields the reducing material, assumed by him to be a keto-aldehyde. For the two forms which he imagines exist he has devised the following formulæ, which may possibly be established when any definite evidence in their support is produced:—

---

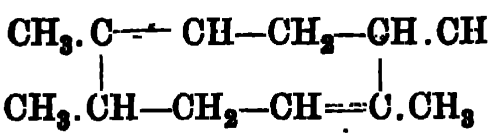
[1] Ostromisslenski, *J. Russ. Phys. Chem. Soc.*, 1916, **48**, 1071.

[2] Harries, *Annalen*, 1911, **383**, 184.

[3] "Unter diesen wurde ein Produkt festgestellt, welches ich fur Methylglyoxal ansprechen möchte."



Normal form giving
Acetonylacetone.



By-product giving a
Keto-aldehyde.

Further results were given in a later paper.[1] An examination of the rate of decomposition of various ozonides was carried out by the following method. About 10 grammes of the ozonide were suspended in 100 grammes of water and heated under a reflux to 120°-125° C. Every quarter (or half) hour the mixture was shaken until the ozonide stuck to the walls of the vessel; the clear liquid was then poured off; the vessel and ozonide were dried for some hours *in vacuo* and then weighed: the decanted liquid was poured back and a fresh experiment begun. From the loss of weight in the ozonide the amount of decomposition was calculated.

Harries states that the rates of ozonide decomposition were similar for natural rubber and for autopolymerized isoprene. Divergency was noted in the case of a rubber obtained from piperylene, $CH_3 . CH : CH . CH : CH_2$, which is not astonishing in view of the fact that piperylene-rubber gives ozonide decomposition products differing entirely from those of natural rubber.

The decomposition curves of the ozonides derived from the rubbers obtained by the sodium-polymerization process differ, according to Harries, from the curve for the ozonide of natural rubber; but it must be noted that he himself points out that even natural rubbers differ among themselves in the readiness with which they form ozonides.

The same method has been applied to the case of synthetic 1 : 5-cyclo-octadiene; and Harries states that its ozonide breaks down at almost exactly the same rate as the ozonide of butadiene-rubber. From this he claims to have proved that his eight-membered ring hypothesis is correct; but it appears that if Pickles' postulates as to the structure of the ozonide were applied to this case the argument for his formula would hold just as well. The matter must therefore be regarded as *sub judice*, the more so since the real value of the decomposition-velocity method is by no means thoroughly tested yet.

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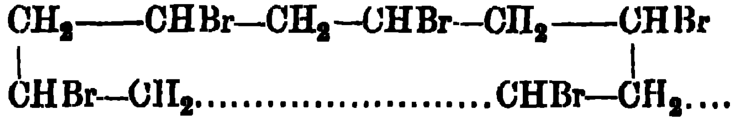
[1] Harries, *Annalen*, 1912, 395, 211.

Ostromisslenski[1] has obtained by the polymerization of vinyl bromide a material which he terms caouprene bromide. This exists in three forms $\alpha \rightarrow \beta \rightarrow \gamma$ which, when submitted to the action of ultra-violet light, are capable of change in the direction shown by the arrows. Boiling with anhydrous acetic acid has a similar effect. The bromide of Harries' butadiene-rubber, which also exists in three modifications, is either identical or isomeric with caouprene bromide. Ostromisslenski does not accept Harries eight-membered ring hypothesis, but regards caouprene bromide as constituted in the following manner :—



$$\begin{array}{l} CH_2\text{——}CHBr\text{—}CH_2\text{—}CHBr\text{—}CH_2\text{——}CHBr \\ | \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad | \\ CHBr\text{—}CH_2\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots CHBr\text{—}CH_2\ldots \end{array}$$

where the dotted line represents an unknown number of —CH_2.CHBr— groups. Both caouprene bromide and butadiene-rubber bromide, when treated with zinc dust, yield the same rubber, apparently butadiene-rubber.

The work of Ostromisslenski[2] has been so fertile in this field during recent years that it seems regrettable that his papers are published in a language which few British chemists can read. He has apparently made a very complete investigation of the methods of preparing butadiene, no fewer than twenty-nine of these being described in a single paper.

Ostromisslenski differs from Harries with regard to the classification of the rubber-like materials produced by synthetic methods. In his view, the physical properties of the product are better indices of its nature than the results of decomposition-reactions have proved to be. For example, a determination may be made of the temperatures at which an artificial rubber acquires and loses its elastic properties ; and if these temperatures agree approximately with those for natural rubber, Ostromisslenski considers that the synthetical substance is "normal." If, on the other hand, there is little agreement here and if the range of temperature over which the artificial product remains elastic is different from the range found for natural rubber, then the artificial product would be regarded as " abnormal."

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[1] Ostromisslenski, *J. Russ. Phys. Chem. Soc.*, 1912, 44, 204.

[2] Ostromisslenski, *J. Russ. Phys. Chem. Soc.*, 1915, 47, 1374, 1472, 1494, 1507, 1926, 1932, 1937, 1941.

The complexity of the processes whereby synthetic rubbers are formed is well illustrated by some of Ostromisslenski's results. When isoprene is kept at a temperature of 80°–90°, it forms an open-chain dimeric form named β-myrcene. This substance, on polymerization by the sodium process, yields a "normal" rubber; whereas isoprene itself, when treated with sodium, gives rise to an "abnormal" polymer.

$$\begin{tikzcd}
\text{Isoprene} \quad C_5H_8 \arrow[r, "\text{Sodium}"] \arrow[d] & \text{Abnormal rubber} \\
\beta\text{-Myrcene} \; C_{10}H_{16} \arrow[r, "\text{Sodium}"] & \text{Normal rubber}
\end{tikzcd}$$

Lebedeff[1] has investigated the polymerization of divinyl derivatives containing conjugated double bonds. The reaction products contain cyclohexene compounds as well as a resinous material derived from cyclo-octadiene. Low temperatures and the action of light favour the formation of the cyclo-octadiene compounds: while cyclohexene derivatives are produced at higher temperatures. Substances of the allene type give rise to cyclobutane compounds.

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[1] Lebedeff, *J. Russ. Phys. Chem. Soc.*, 1910, **42**, 949; 1911, **43**, 820.

CHAPTER VI

THE ALKALOIDS

A.—GENERAL.

WHEN we attempt to define what we mean by the term "alkaloid" our difficulties are not small. On the one hand, our definition may be so drawn as to include almost every naturally occurring nitrogen-compound, which is obviously useless as a mode of classification; or it may be so narrow as to exclude some of the most important of the substances which are usually included in the alkaloid group. The most general definition is perhaps the best; and for our present purpose we shall treat as alkaloids those naturally occurring substances which contain cyclic chains, of which at least one member is a nitrogen atom. This definition opens to us a much wider field than we can possibly attempt to cover in the space at our disposal, and in the following pages we shall aim at describing the syntheses and constitutions of a few typical compounds rather than at a survey of the whole subject.

Practically all the important alkaloids are found in the tissues of vegetables; and if we except xanthine derivatives, we might have modified the definition given above by limiting the term "alkaloid" to basic substances found in plants.

As the following pages will show, the chemistry of the alkaloids resembles that of the aromatic compounds, in that each class seems to be built up upon the basis of one substance. In the aromatic series benzene lies at the root of all the compounds, however complicated they be; whilst in the alkaloids pyridine appears to be equally essential. And just as among the aromatic types we find a benzene ring condensed with other cyclic chains, so in the alkaloids we may discover compounds in which the pyridine ring is overlaid with others. Even the derivatives of the purine group may be considered to be derived from pyridine by the introduction of a second nitrogen atom into the ring.

With regard to the occurrence of the alkaloids in nature, very little generalization is possible. The monocotyledons seem to be richest in members producing alkaloids; while among the cryptogamia there appears to be no alkaloid-formation. Just as little regularity is found with regard to the distribution of the alkaloids in the various portions of the plant structure, but alkaloids are chiefly found in the fruits and sap or, in the case of trees, in the bark.

Since in most cases alkaloids occur as salts, they are obtained from the actual plant tissues by the action of alkali, which liberates the basic part of the molecule. If this be volatile in steam, the alkaloid is obtained in this way; but if it be not thus volatile it is extracted from the tissues by treating them with acids, which dissolve the alkaloids, forming solutions of their salts, from which the free alkaloid is obtained by the action of alkali. Final purification is carried out by crystallization of the alkaloid or of its salts. When extraction is carried out on a small scale, chloroform is often used to remove alkaloids from the tissues in which they occur.

The majority of alkaloids are solid substances, but one or two are liquids which can be distilled without decomposition. Nearly all of them have powerful actions upon the animal organism; but owing to our ignorance of the relation between chemical constitution and physiological action, not much can be said on the subject. In most cases alkaloids are found to possess lævo-rotation, and it is very seldom that both optically active forms are found in nature.

B.—METHODS EMPLOYED IN THE DETERMINATION OF ALKALOID CONSTITUTIONS.

After we have carried out an elementary analysis of an alkaloid we are in a position to state its percentage composition, and by a molecular weight determination we can estimate the number of atoms which its molecule contains. The next step is the determination of the mode in which these atoms are linked together in the alkaloid molecule, and we shall now give a brief account of some common reactions which are employed to solve this problem.

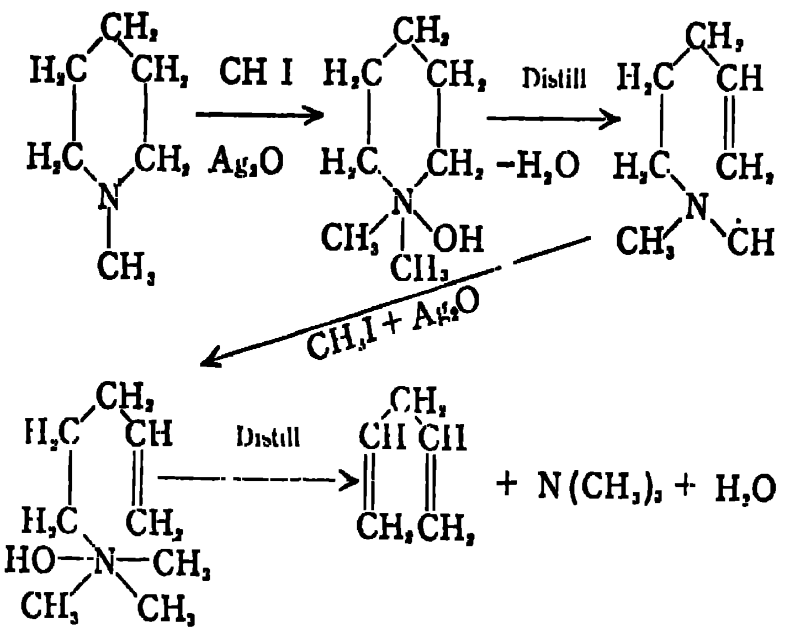
In the first place, since many alkaloids are known to be esters it is usual to employ some hydrolytic method in order to see whether or not the alkaloid molecule can be decomposed into some simpler grouping. To this end the alkaloid may be heated with water, acids, or alkalis until it is decomposed into its component acid and base. This method, while breaking up any salt or ester, does not, except in a few cases, result in any further destruction of the body, so that from the constitutions of the two halves we are able to deduce the constitution of the parent substance.

This method of decomposition, however, may not carry us far enough, and it is usually seconded by a more violent action. For instance, the alkaloid may be fused with alkali, distilled with zinc dust, heated with bromine or phosphoric acid. When reagents such as these are employed, the less durable part of the molecule is usually shattered, and in the reaction-product we find some stable nucleus such as pyridine, quinoline, or isoquinoline from which the whole alkaloid is derived.

Again, many alkaloids exist in the form of methyl ethers. These can be broken up by boiling with hydriodic acid (*Zeisel's* method), and by passing the methyl iodide thus formed into silver nitrate solution the number of methyl radicals split off by the hydriodic acid may be estimated, and thus the number of methoxyl groups in the alkaloid can be ascertained.

When the alkaloid contains an oxygen atom, it is of importance to determine whether this occurs in a carbonyl, carboxyl, hydroxyl, or other group. The first is determined in the usual way by the action of phenylhydrazine or hydroxylamine, the hydroxyl group can usually be detected by acylating it or by the action of dehydrating agents, which split off water and leave an unsaturated substance, while if the alkaloid is an alkyl ether it can often be decomposed by Zeisel's method. If the carboxyl group occurs in the alkaloid under examination, there is not much difficulty in detecting its presence.

All alkaloids contain nitrogen, but it is necessary to discover in what way this nitrogen is linked with the rest of the molecule. Herzig and Meyer have devised a method of determination for methyl imino groups which is very useful in this branch of research. The hydriodides of bases in which a methyl group is attached to nitrogen, when heated to about 300° C., split off methyl iodide, which can be estimated with silver nitrate just as in the case of the methoxyl group. A somewhat similar decomposition results in the reaction which is usually termed "exhaustive methylation." Here, by the action of methyl iodide and silver oxide, assisted by dry distillation, a cyclic nitrogen compound may be made to lose its nitrogen atom with but little alteration in the rest of the molecule. The formulæ will make the process clear without further explanation :—



The final stages in determining the constitution of any alkaloid are usually those in which the oxidation products of the substance are studied. All the agents employed are well-known, so it is unnecessary to describe their actions. The most useful are potassium permanganate, hydrogen peroxide, dilute nitric acid and chromic acid.

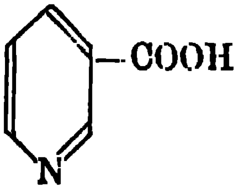
C.—The Pyrrolidine Group.

1. *Nicotine.*

The alkaloid nicotine stands in a position midway between the pyridine and the pyrrolidine groups; for, as will be shown presently, it contains both a pyridine and a pyrrolidine nucleus. It therefore forms a convenient bridge by which we can pass from the consideration of the one class to the other.

Nicotine is a basic substance having the composition $C_{10}H_{14}N_2$. Its constitution has been established by means of the following reactions:—

1. Nitric acid, chromic acid, or potassium permanganate oxidize nicotine[1] to nicotinic acid—

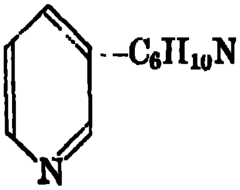


2. By the action of bromine upon nicotine, two derivatives[2] are formed—

   (*a*) Dibromocotinine, $C_{10}H_{10}Br_2N_2O$.
   (*b*) Dibromoticonine, $C_{10}H_8Br_2N_2O_2$.

3. When dibromocotinine is decomposed by bases it gives methylamine, oxalic acid, and a compound C_7H_7NO. By the same treatment dibromoticonine yields methylamine, malonic, and nicotinic acids.
4. Nicotine is a di-tertiary base,[3] giving two isomeric methyl iodide addition products.

From the first reaction it is obvious that nicotine must be pyridine, with a side-chain in the β-position.



From the third reaction it is clear that of the two nitrogen atoms in nicotine, one carries a methyl group. This one cannot be the pyridine nitrogen. Further, the second nitrogen atom (which *does* carry the methyl radicle) cannot belong to a pyridine ring. We may thus go a step further, and represent nicotine by the formula—

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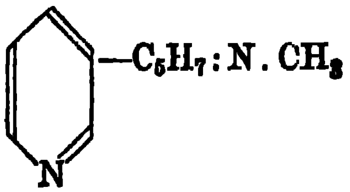
[1] Huber, *Annalen*, 1867, **141**, 271; Weidel, *Annalen*, 1873, **165**, 328; Laiblin, *Ber.*, 1877, **10**, 2136.
[2] Pinner, *Ber.*, 1893, **26**, 292.
[3] Pictet and Genequand, *Ber*, 1897, **30**, 2117.



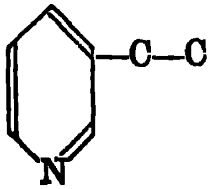
Again, the third reaction shows us that dibromocotinine and dibromoticonine give rise to three carbon chains—

$C—CH_2—C$

Malonic acid chain.

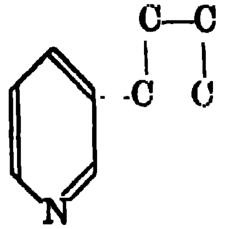
$—C.C—$

Oxalic acid chain.

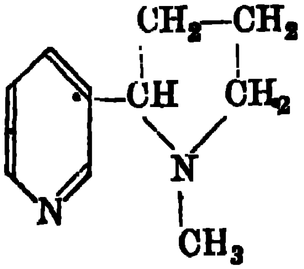


C_7H_7NO chain.

These must be somehow combined in the nicotine molecule, so we may write the nicotine skeleton thus—



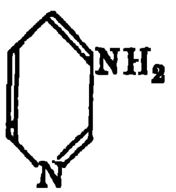
To this we must attach the group: $=N.CH_3$ in some way. From the fourth reaction we deduce that this nitrogen atom is a tertiary one, so that the two isomeric methyl iodide addition products may be explained by the addition of methyl iodide to a different nitrogen atom in each case. But if the group $:N.CH_3$ is to contain a tertiary nitrogen atom, and also to be attached to the nicotine skeleton given above, the only way is to make the nitrogen atom a member of a ring. The constitution of nicotine would then be—



Nicotine.

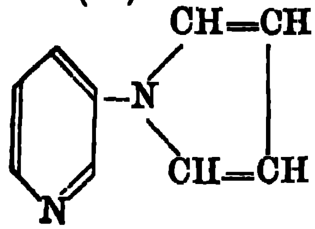
The synthetic preparation of nicotine proved to be a much harder task than was anticipated. The first steps were taken by Pictet and Crépieux,[1] who, by heating β-amido-pyridine (I.) with mucic acid, were able to produce (II.) N-β-pyridyl-pyrrol. Like many other N-alkyl derivatives of pyrrol, this substance when passed through a heated tube undergoes a molecular rearrangement, in the course of which the pyridine group is transferred to the carbon atom next the nitrogen in the pyrrol ring. The compound thus formed is *a*β-pyridyl-pyrrol (III.)—

(I.)



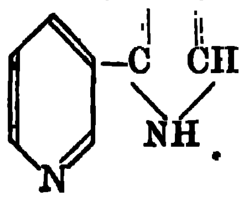
β-amido-pyridine.

(II.)



N-β-pyridyl-pyrrol.

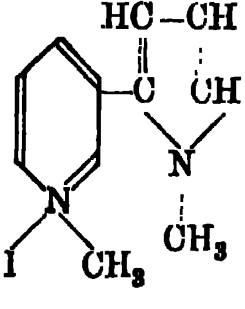
(III.)



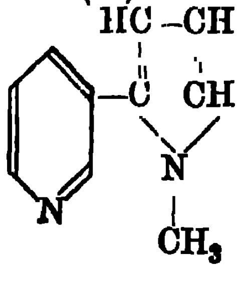
β-pyridyl-*a*-pyrrol.

From this substance Pictet[2] continued the synthesis in the following way. The *a*β-pyridyl-pyrrol forms a potassium salt, the imino-hydrogen of the pyrrol group being replaced in the usual way by the metallic atom; and from this salt, by the action of methyl iodide, we obtain the methyl derivative of the iodomethylate (IV.). On distillation with lime, this forms the base nicotyrine (V.)—

(IV.)



(V.)



Nicotyrine.

Now, this body cannot be reduced direct to nicotine, for any agent which attacks the pyrrol nucleus will, at the same time, reduce the pyridine ring. The transformation can be carried out in the following way, however. The nicotyrine (V.) is treated with iodine in alkaline solution, by which means a mono-iodine derivative is produced; it in turn is acted on by tin and hydrochloric acid, whereby it is partially reduced, forming dihydro-nicotyrine (VI.). This substance reacts with bromine to form a perbromide, $C_5H_4N . C_5H_8N . Br_4$, which, by reduction with tin and hydrochloric acid, yields inactive nicotine (VII.). This racemic base can, like coniine, be resolved into its antipodes by means of tartaric acid; so that in this way the synthesis of lævo-nicotine, corresponding to the natural alkaloid, can be accomplished –

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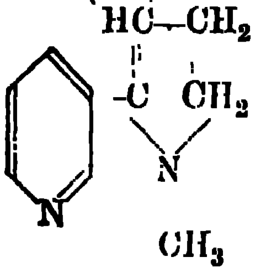
[1] Pictet and Crépieux, *Ber.*, 1895, 28, 1904.

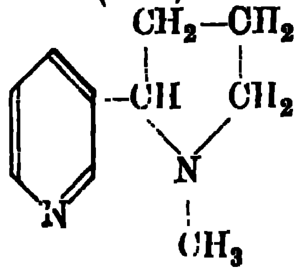
[2] Pictet, *Compt. rend.*, 1903, 137, 860.

(VI.)



Dihydro-nicotyrine.

(VII.)



Nicotine.

2. *Tropinone, Tropine, and ψ-Tropine.**

Hitherto we have confined our attention to compounds which contain isolated rings of carbon and nitrogen atoms; but with the tropine series we enter a new class in which we shall have to deal with bridged rings analogous to those of the dicyclic terpenes. The first member of the group is tropinone.

This substance was originally prepared by an extremely roundabout method;[1] but a new direct synthesis has been devised by Robinson,[2] so that it is unnecessary to describe the older method, which involved nearly twenty stages.

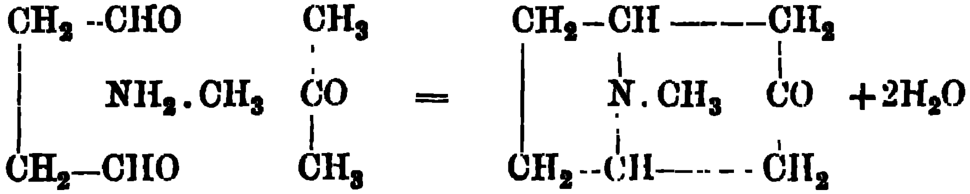
Succindialdehyde (obtained from succindialdoxime and nitrous fumes) was allowed to interact in aqueous solution with methylamine and acetone for half an hour, when it was found that tropinone was formed—

---

* The Greek ψ is used instead of the word "pseudo." Thus ψ-tropine represents pseudo-tropine.

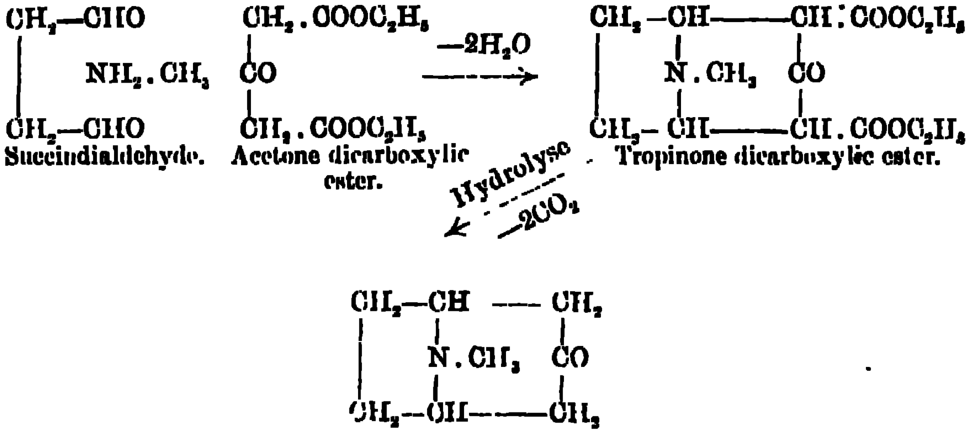
[1] Willstätter, *Annalen*, 1901, 317, 268; 1903, 326, 1; *Ber.*, 1901, 33, 3163; Willstätter and Iglauer, *ibid.*, 1900, 33, 1170.

[2] Robinson, *Trans.*, 1917, 111, 762.



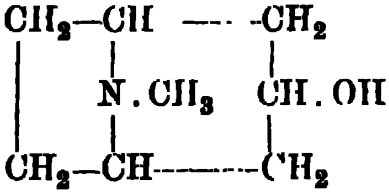
Succindialdehyde. Acetone. Tropinone.

Better yields can be obtained by substituting for acetone the ester or calcium salt of acetone dicarboxylic acid. The intermediate product is a tropinone dicarboxylic acid from which two molecules of carbon dioxide can be split off by acidifying and heating the solution—



Succindialdehyde. Acetone dicarboxylic ester. Tropinone dicarboxylic ester. Tropinone.

From tropinone, tropine itself can be obtained[1] by the action of zinc dust and concentrated hydriodic acid—



Tropine.

The isomerism of tropine and ψ-tropine may be explained very simply. If the space formula of a compound having the constitution of tropine be built up, it will be found that there are two possibilities: the hydroxyl and the methyl groups may lie on the same side of the ring as in (A), or on opposite sides as in (B)—

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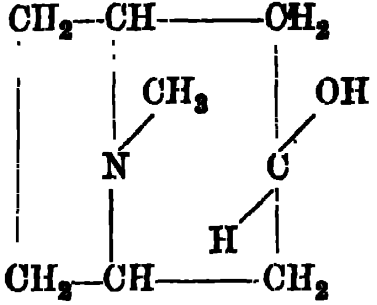
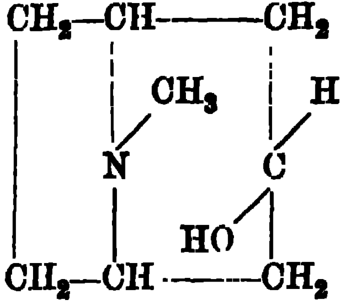
[1] Willstätter and Iglauer, *Ber.*, 1900, 33, 1170.

(A.)



(B.)

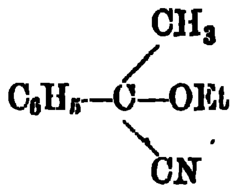


Of the two, tropine is the labile isomer, so that we can convert it at will into ψ-tropine.

3. *Tropic Acid.*

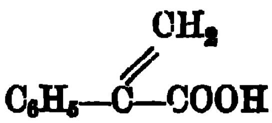
By the synthesis of tropine we have approached that of another alkaloid, atropine. This substance, when boiled with baryta water, breaks down into tropine and tropic acid. We have thus established the constitution of half the atropine molecule; and in the present section we shall deal with the constitution of the other portion.

Tropic acid has been synthesized by Ladenburg and Rügheimer.[1] Acetophenone is treated with pentachloride of phosphorus, whereby the oxygen atom is replaced by two chlorine ones, and acetophenone chloride is formed. This is allowed to react with potassium cyanide in alcoholic solution to form the nitrile of atrolactinic ethyl ether—



$$C_6H_5-\overset{\displaystyle CH_3}{\underset{\displaystyle CN}{C}}-OEt$$

The nitrile is then hydrolysed, forming the acid. When this body is boiled with concentrated hydrochloric acid it loses alcohol, and is converted into atropic acid—



$$C_6H_5-\overset{\displaystyle CH_2}{\overset{\|}{C}}-COOH$$

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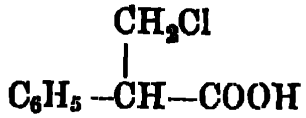
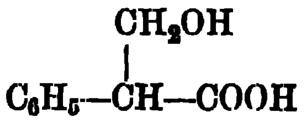
[1] Ladenburg and Rügheimer, *Ber.*, 1880, 13, 876, 2041.

Hydrochloric acid then attaches itself to the double bond, yielding β-hydrochloratropic acid—



$$C_6H_5-\overset{\overset{\displaystyle CH_2Cl}{|}}{C}H-COOH$$

This substance, when boiled with potassium carbonate, exchanges a chlorine atom for a hydroxyl group, and is converted into tropic acid—

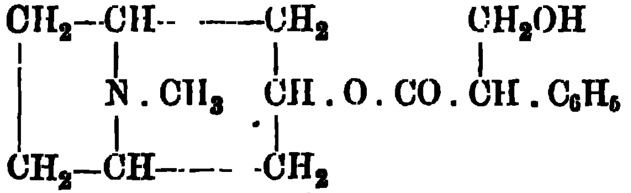


$$C_6H_5-\overset{\overset{\displaystyle CH_2OH}{|}}{C}H-COOH$$

Tropic acid.

4. *Atropine.*

The constitutions of the two halves of the atropine molecule have now been established, and the atropine synthesis can be carried out by treating a mixture of tropine and tropic acid with hydrochloric acid gas in the usual way.[1] Atropine, therefore, is the tropine ester of tropic acid, and it must have the constitution shown by the following formula:—



Atropine.

5. *Ecgonine.*

Tropinone forms salts with alkalis, and these, by treatment with carbon dioxide in the usual way, can be converted into the alkali salts of carboxylic acids.[2] In the case of the sodium salt, it is suspended in ether, and carbon dioxide is passed through the liquid at ordinary temperatures; the resulting product is the sodium salt of tropinone carboxylic acid, and when this is reduced with sodium amalgam in a weakly acid

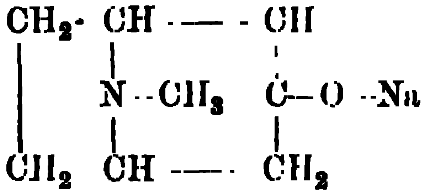
[1] Ladenburg, *Ber.*, 1879, **12**, 941; 1880, **13**, 104.

[2] Willstätter and Bode, *Ber.*, 1900, **33**, 411.

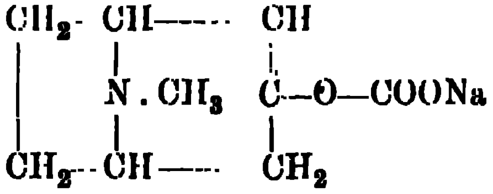
solution it yields a mixture of two isomeric bodies having the same composition as ecgonine, $C_8H_{14}NO \cdot COOH$.

The two isomers, however, differ in character. The one has all the properties of ecgonine, except the power of rotating the plane of polarization; it is a true carboxylic acid, forming salts and esters, it also possesses a free hydroxyl group, and can be converted into esters by acids. The second isomer, on the other hand, behaves quite differently. It possesses no free hydroxyl group; nor can it be esterified by the ordinary methods. An explanation of the formation of two such substances is to be found by considering the character of the sodium derivative of tropinone.

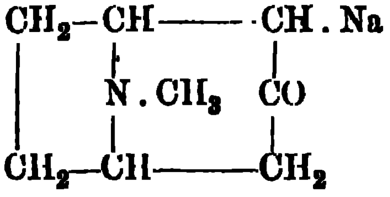
It is well known that the sodium salts of ketonic bodies usually exist in the enolic form, so that we should incline to write the formula of the tropinone sodium salt thus—

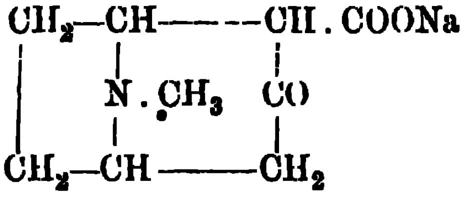


The action of carbon dioxide upon this would produce a sodium salt whose constitution could be written—

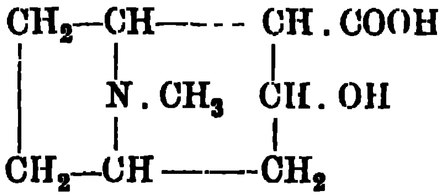


This body forms by far the greater proportion of the reaction mixture, but since the sodium salt of tropinone exists in the keto- as well as in the enol-form, part of the end-product will have the constitution shown below—





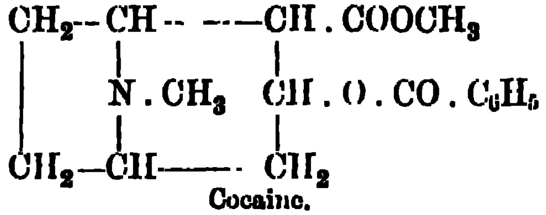
This last substance, on reduction, would give us the alcohol—



which proves to be racemic ecgonine.

6. *Cocaine.*

From ecgonine, cocaine can be prepared by benzoylating the alcohol radicle, and then esterifying the carboxyl group with methyl alcohol—



Cocaine.

D.—THE QUINOLINE GROUP.

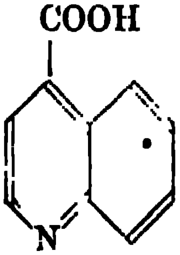
1. *The Constitution of Cinchonine.*

The alkaloid cinchonine has the composition $C_{19}H_{22}ON_2$. The oxygen atom forms part of a hydroxyl group, as is shown by acetylation; and the two nitrogen atoms are tertiary ones.

I. When cinchonine is oxidized by means of chromic acid and sulphuric acid[1] it breaks down into two substances, cinchonic acid and meroquinone, in accordance with the following equation:—

$$\underset{\text{Cinchonine}}{C_{19}H_{22}ON_2} + 3O = \underset{\text{Cinchonic acid.}}{C_{10}H_7O_2N} + \underset{\text{Meroquinone.}}{C_{19}H_{15}O_2N}$$

Cinchonic acid has been shown to be a quinoline carboxylic acid of the formula—



so that cinchonine itself must be a γ-quinoline derivative.

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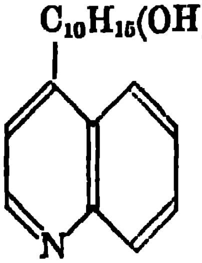
[1] Königs, *Ber.*, 1894, 27, 1501.

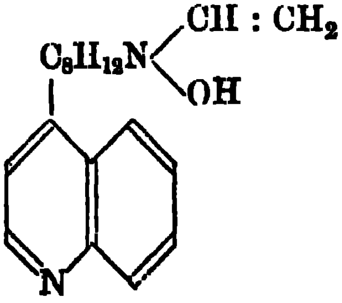
For the sake of convenience, we will refer to the two halves of the cinchonine molecule as the "quinoline half" and the "second half." It is obvious that the hydroxyl group which is known to exist in the cinchonine molecule must be situated in the "second half"; for if it were in the "quinoline half" it would appear in cinchonic acid. We may therefore formulate cinchonine in the following way:—



II. Now, when cinchonine is oxidized with potassium permanganate[1] instead of chromic acid, the decomposition products are quite different from those obtained before. The reaction takes the course shown below—

$$\underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} + 4O = \underset{\text{Cinchotenine.}}{C_{18}H_{20}O_3N_2} + H.COOH$$

This new oxidation product, cinchotenine, contains the quinoline nucleus (as is shown by its behaviour on further oxidation). It is therefore produced by a decomposition in the "second half" of the molecule. It contains a hydroxyl and a carboxyl group. Cinchonine can take up one molecule of a halogen acid, but cinchotenine has lost this property. Hence the group CH_2 of cinchonine has been split off, leaving the carboxyl group in cinchotenine. We may thus carry our deductions a step further, and write the formula of cinchonine in the following way:—



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[1] Königs, *Annalen*, 1879, 197, 374.

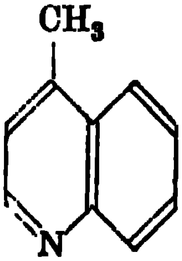
III. We must now turn to a different reagent. When cinchonine is treated with phosphorus pentachloride and then with alcoholic potash it loses a molecule of water and is converted into cinchene [1]—

$$\underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} - H_2O = \underset{\text{Cinchene.}}{C_{19}H_{20}N_2}$$

When heated with 25 per cent. phosphoric acid,[2] cinchene takes up two molecules of water and is decomposed into lepidine and meroquinene—

$$\underset{\text{Cinchene.}}{C_{19}H_{20}N_2} + 2H_2O = \underset{\text{Lepidine.}}{C_{10}H_9N} + \underset{\text{Meroquinene.}}{C_9H_{15}O_2N}$$

Lepidine is known to have the formula—



IV. Meroquinene is the next substance whose decompositions must be examined. When it is oxidized with an ice-cold mixture of sulphuric acid and potassium permanganate it gives cincholoiponic acid [3]—

$$\underset{\text{Meroquinene.}}{C_9H_{15}O_2N} + 4O = \underset{\text{Cincholoiponic acid.}}{C_8H_{13}O_4N} + H\,.\,COOH$$

This, by the action of aqueous permanganate, is converted into loiponic acid [4]—

$$\underset{\text{Cincholoiponic acid.}}{C_8H_{13}O_4N} + O_2 = \underset{\text{Loiponic acid.}}{C_7H_{11}O_4N} + H\,.\,COOH$$

Loiponic acid is an unstable form of hexahydrocinchomeronic acid, for on heating with caustic potash it is converted into that substance by isomeric change. By assuming the *structure* of loiponic acid to be the same as that of hexahydrocinchomeronic acid (the *configurations* of the two being different), we can work back step by step to meroquinene, whose formula must therefore be that shown in the series below—

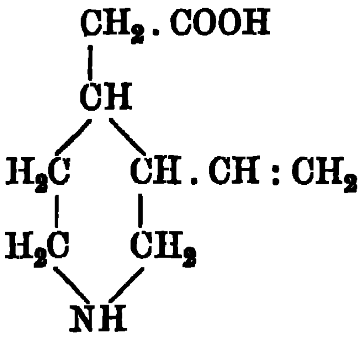
---

[1] Comstock and Königs, *Ber.*, 1884, **17**, 1985.

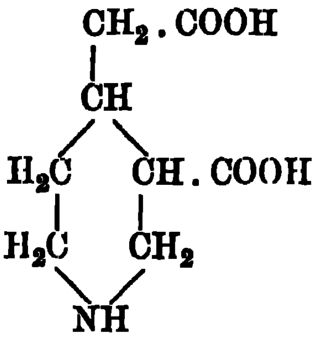
[2] Königs, *Ber.*, 1890, **23**, 2677; 1894, **27**, 900.

[3] *Ibid.*, 1895, **28**, 1986, 3150.

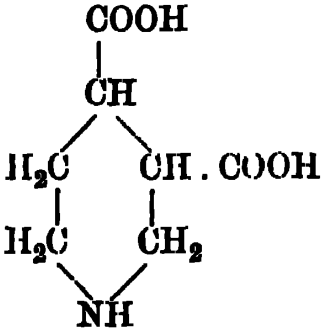
[4] Skraup, *Monatsh.*, 1896, **17**, 377; Königs, *Ber.*, 1897, **30**, 1329.



Meroquinene.



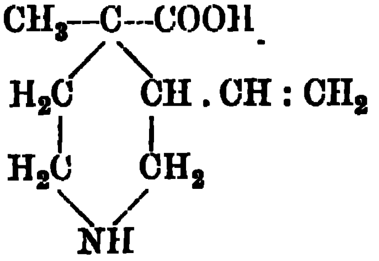
Cincholoiponic acid.



Loiponic acid.

The position of the $—CH_2.COOH$ group of meroquinene is uncertain.

The formula above is due to Königs, but the alternative put forward by Miller and Rohde[1]—



has probably as much to recommend it.

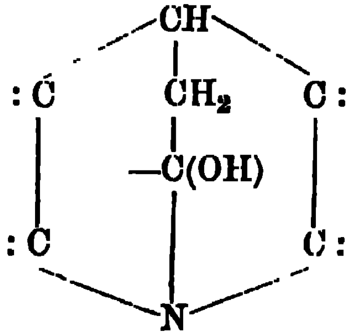
Of the ten carbon atoms of the "second half" we have thus established the mode of linkage of eight: five in a piperidine ring, two in a vinyl group, and one in a methyl or methylene group. The ninth carbon atom of the "second half" must be utilized in joining the two halves together. Thus we have only to determine the position of the tenth carbon atom of the "second half."

---

[1] Miller and Rohde, *Ber.*, 1895, 28, 1060.

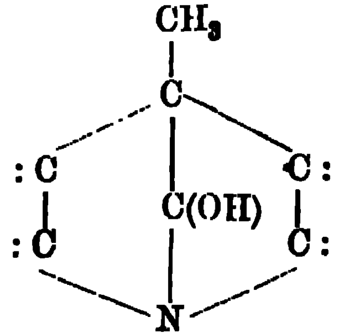
V. It will be remembered that the two nitrogen atoms of cinchonine are tertiary; but it has been shown that the nitrogen atom of meroquinene is a secondary one. This has been established by the usual reactions of the imido group, and agrees with the constitution which we have ascribed to meroquinene in the previous paragraph. This peculiar behaviour of the nitrogen atom can best be explained by the assumption that in the "second half" of cinchonine we have a nucleus of either of the types (I.) or (II.)—

Königs' view.



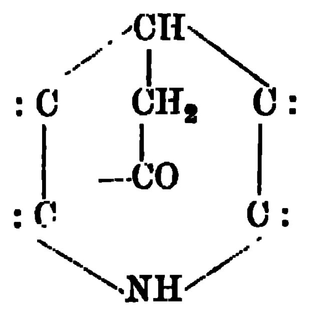
(I.)

v. Miller's view.

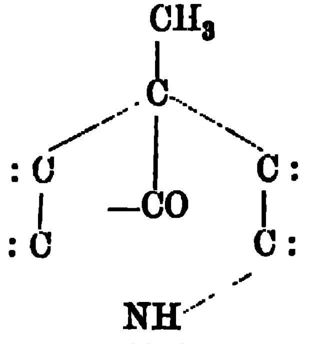


(II.)

When such a nucleus as (I.) is heated with dilute acids it will undergo intramolecular change into an imido-ketone in the way expressed by the formula (I*a*.) below. If the type (II.) be chosen instead of (I.) the analogous substance (II*a*.) would be produced in the same way—



(I*a*.)



(II*a*.)

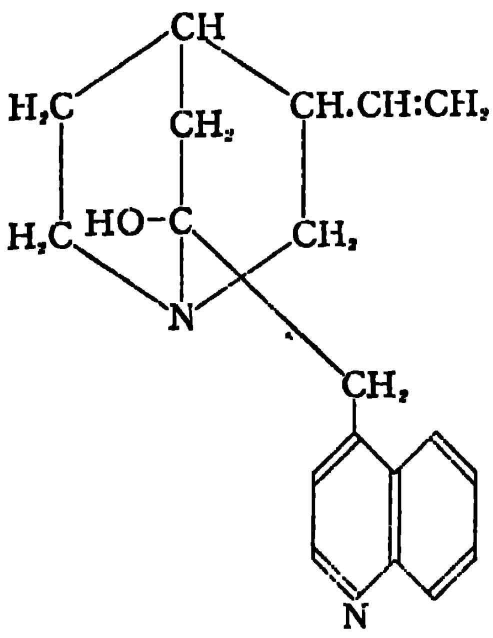
Such a change actually occurs when cinchonine is heated with dilute acetic acid; an imido-ketone results, which, on account of its poisonous properties, is named "*cinchotoxine*." [1]

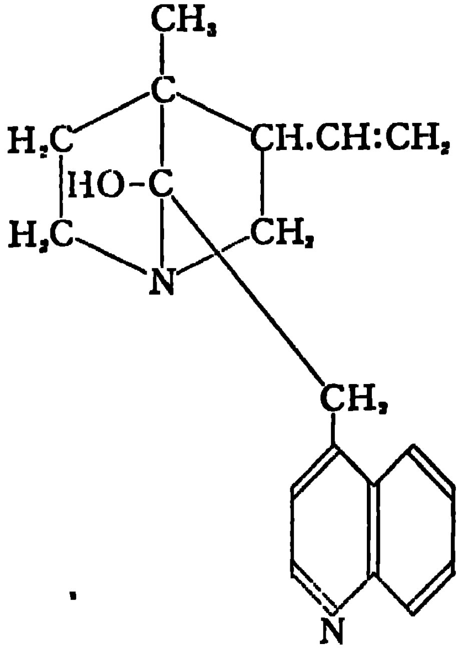
---

[1] Miller and Rohde, *Ber.*, 1894, **27**, 1187, 1279; 1895, **28**, 1056.

Thus it is apparent that across the piperidine ring there is a bridge of one carbon atom, and this accounts for the missing tenth carbon atom in the "second half" of cinchonine.

From the foregoing evidence, cinchonine would be represented by either of the two formulæ below—





2. *The Constitution of Quinine.*

Knowing the constitution of cinchonine, we can easily prove that of quinine.

I. Quinine differs from cinchonine by one carbon, one oxygen, and two hydrogen atoms—

$$\underset{\text{Quinine.}}{C_{20}H_{24}O_2N_2} - \underset{\text{Cinchonine.}}{C_{19}H_{22}ON_2} = CH_2O$$

This points to quinine being a methoxy derivative of cinchonine, if we bear in mind the similarity in character between the two substances.

II. When oxidized with sulphuric and chromic acids,[1] quinine gives the acid (A); whereas it will be remembered that cinchonine gave cinchonic acid (B). Meroquinene is one of the oxidation products in both cases—

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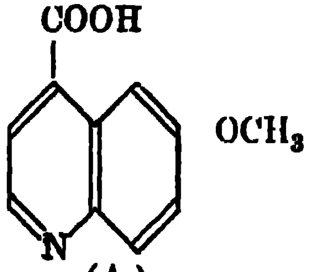
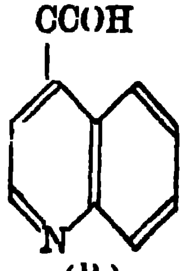
[1] Skraup, *Monatsh.*, 1881, **2**, 591; 1883, **4**, 695; 1891, **12**, 1106; 1895, **16**, 2684.

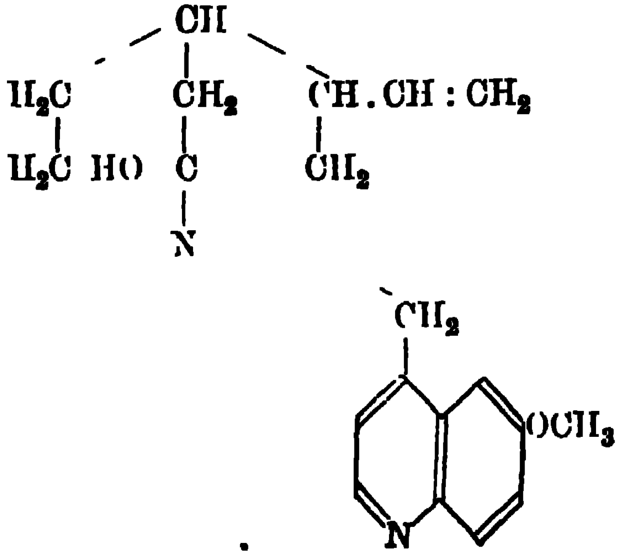


(A.)



(B.)

III. This proves the presence and position of the methoxyl group in quinine; and since in its reactions quinine forms an exceedingly close analogue to cinchonine, we are justified in concluding that it is a methoxy cinchonine of the following constitution (accepting Königs' view of the structure of cinchonine):—



Quinine

3. *Cinchonidine and Conchinine.*

Cinchonine has three asymmetric carbon atoms in its molecule, and therefore it may occur in several stereoisomeric forms. Chinchonidine is supposed to be one of these; while conchinine is a stereoisomer of quinine.

E.—The Isoquinoline Group.

1. *The Constitution of Papaverine.*

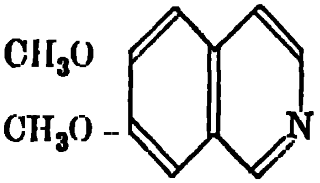
The constitution of papaverine is a much simpler question than that with which we have just dealt in the case of cinchonine. There are six steps in the argument.[1]

---

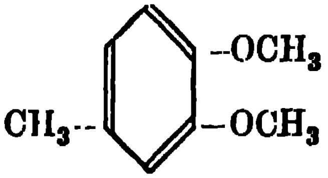
[1] Goldschmiedt, *Monatsh.*, 1883, 4, 704; 1885, 6, 372, 667, 954; 1886, 7, 485; 1887, 8, 510; 1888, 9, 42, 327, 349, 679, 762, 778; 1889, 10, 673, 692.

I. In the first place, the formula of papaverine is $C_{20}H_{21}O_4N$; it contains four methoxyl groups, which can be hydrolysed, yielding the substance papaveroline, $C_{16}H_9N(OH)_4$. This accounts for all the oxygen atoms.

II. On fusion with alkali, papaverine breaks down into two nuclei, one of which contains nitrogen, while the other nucleus is nitrogen-free. The first was proved to be a dimethoxyquinoline of the constitution—



while the second decomposition product was dimethylhomocatechol—



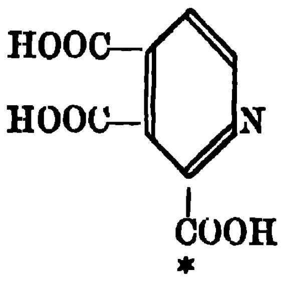
III. The fact that these two groups are *directly* united to one another follows from the composition of the two decomposition products—

$$H_2 + C_{20}H_{21}O_4N = C_{11}H_{11}O_2N + C_9H_{12}O_2$$

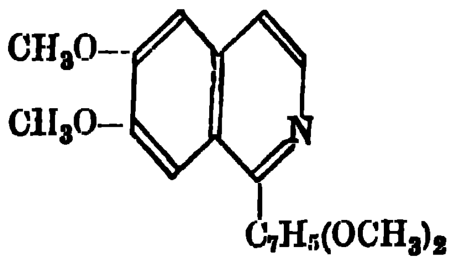
Papaverine. Dimethoxyquinoline. Dimethoxyhomocatechol.

IV. We must now examine the question of the manner in which the two nuclei are united. Since papaverine contains four methoxy groups, and each of the decomposition products contains two, it is obvious that during the decomposition no methoxy group is destroyed. Now, if the link between the two nuclei had been an oxygen atom, *i.e.* if papaverine had contained the grouping R—O—CH_2—O—R, then in the breakdown of the molecule one -O . CH_2 . O- group would have been destroyed. We may therefore exclude the idea of joining the two nuclei through an oxygen atom, and must assume that they are directly united, carbon to carbon.

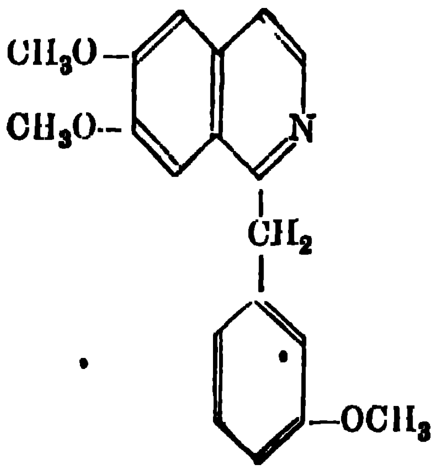
V. Our next problem is to find which carbon atom of the isoquinoline ring is joined to the other nucleus. When we oxidize papaverine with potassium permanganate, we obtain α-carbocinchomeronic acid—



Hence we deduce that the side-chain (second nucleus) was attached at the point now occupied by the carboxyl group, which is marked with an asterisk. Papaverine is therefore—



VI. We have now to settle the constitution of the group —$C_7H_5(OCH_3)_2$. This must be the dimethoxy-homocatechol radicle, which has the same composition. We have only to decide whether the two nuclei are joined ring to ring or by the intermediation of the side-chain of the dimethoxy-homocatechol. Without going into details, it may be said that all the evidence points to the union being made through the side-chain. The constitution of papaverine is therefore—

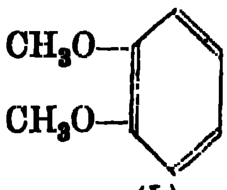


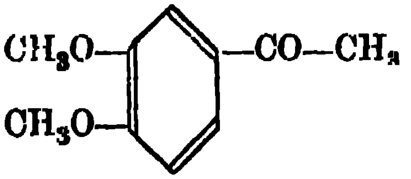
Papaverine.

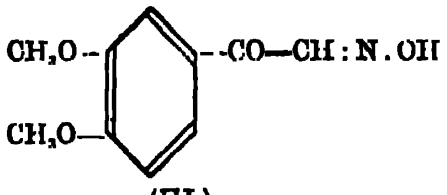
2. *The Synthesis of Papaverine.*

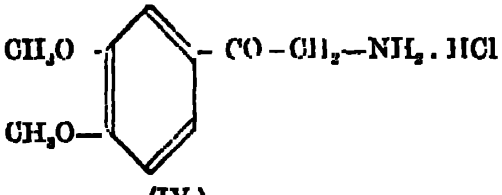
The synthesis of papaverine has recently been carried out by Pictet and Gams.[1] The reactions may be grouped in five stages.

I. The first step in the process is the synthesis of amino-aceto-veratrone. For this purpose veratrol (I.) is treated with acetyl chloride in presence of aluminium chloride, whereby aceto-veratrone (II.) is formed. When this is treated with sodium ethylate and amyl nitrate, it yields the isonitroso-derivative (III.), which can then be reduced by tin chloride and hydrochloric acid to the hydrochloride of amino-aceto-veratrone (IV.)—

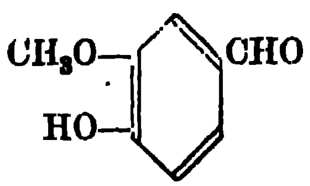

(I.)

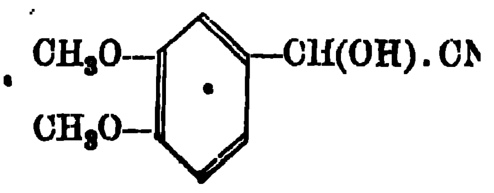

(II.)


(III.)


(IV.)

II. We must now turn to the synthesis of homoveratroyl chloride. Vanillin (V.) is methylated and then treated with hydrocyanic acid, giving dimethoxy-mandelic nitrile (VI.). When this is boiled with hydriodic acid three processes take place simultaneously; reduction, hydrolysis, and the splitting off of methyl radicles. We thus obtain homoprotocatechuic acid (VII.) and by methylation of the hydroxyl groups followed by the action of phosphorus pentachloride the chloride of homoveratric acid is formed (VIII.)—


(V.)


(VI.)

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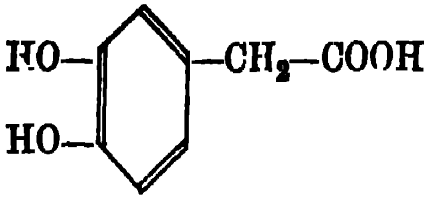
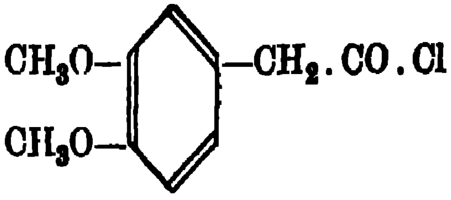
[1] Pictet and Gams, *C. R.*, 1909, 149, 210.

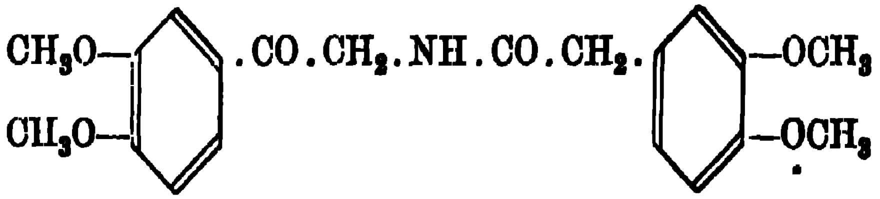


(VII.)



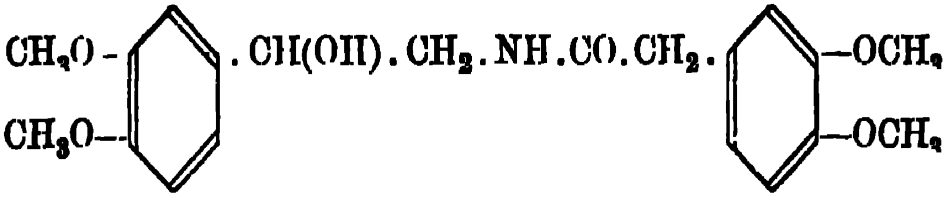
(VIII.)

III. If we now allow the amino-aceto-veratrone hydrochloride obtained in Stage **I.** to interact with the homoveratric chloride of Stage **II.** in presence of alkali, we obtain homoveratroyl-amino-aceto-veratrone (IX.)—



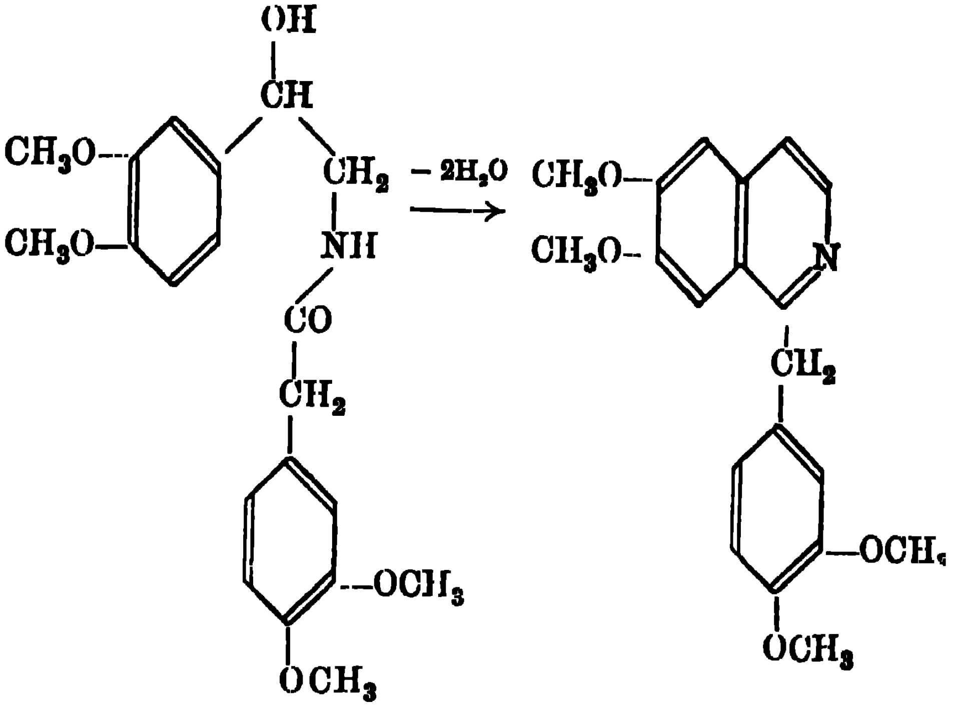
(IX.)

IV. An inspection of the formula (IX.) will show that though the substance contains two carbonyl groups, one of these is a true carbonyl while the other is a radicle which originally formed part of a carboxyl group. When the substance is reduced with sodium amalgam in neutral alcoholic solution, the true carbonyl is reduced, while the acidic carbonyl remains unaffected. The product is homoveratroyl-hydroxyhomoveratrylamine (X.)·



(X.)

V. When this substance (X.) is treated with phosphorus pentoxide in boiling xylene solution, it loses two molecules of water and is converted into papaverine (XI.)—



(X.) (XI.)

3. *The Synthesis of Laudanosine.*

In the preceding section we have seen how the synthesis of papaverine may be accomplished, and we are now in a position to consider the question of a closely related alkaloid, laudanosine. This body is very simply produced from papaverine. Pictet and Athanasescu[1] showed that if we form the chloro-methyl derivative of papaverine and then reduce this with tin and hydrochloric acid we obtain methyl-tetrahydropapaverine. This synthetic substance is of course racemic and from it the dextro-antipode was obtained in the usual way by making the quinic acid salt of the alkaloid and fractionally crystallizing it. The substance thus obtained was found to be identical with natural laudanosine—

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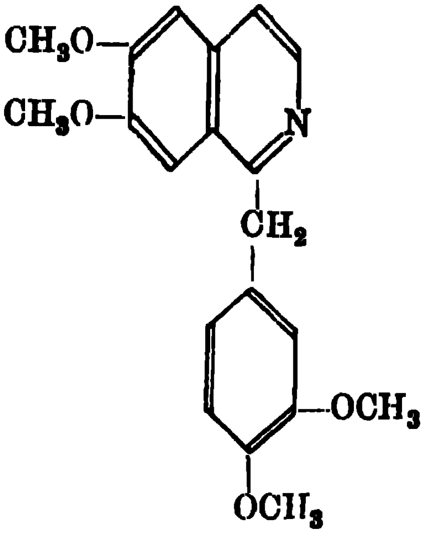
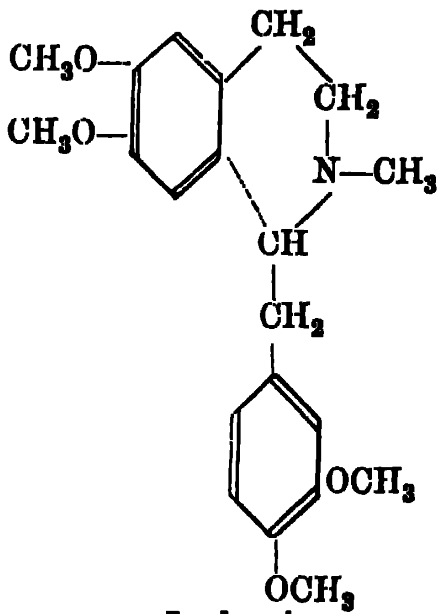
[1] Pictet and Athanasescu, *Ber.*, 1900, 33, 2346.



Papaverine.



Laudanosine.

Pictet and Finkelstein[1] have recently carried out the complete synthesis of laudanosine, but as the method is very similar to that which we have already described in the case of papaverine we need not enter into it here.

4. *Opianic Acid.*

Though opianic acid itself is not an alkaloid, we must take up its constitution at this point owing to its relation with narcotine, with which we shall deal later.

I. When narcotine is hydrolysed with barium hydrate or sulphuric acid,[2] it decomposes into opianic acid and hydrocotarnine—

$$\underset{\text{Narcotine.}}{C_{22}H_{23}O_7N} + H_2O = \underset{\text{Opianic acid.}}{C_{10}H_{10}O_5} + \underset{\text{Hydrocotarnine.}}{C_{12}H_{15}O_3N}$$

II. Opianic acid is a monobasic acid, and therefore we may write its formula $C_9H_9O_3 \,.\, COOH$.

III. When heated with hydriodic acid, two methyl groups are split off from opianic acid.[3] It therefore contains two methoxy groups, and may be written thus, $(CH_3O)_2 \,.\, C_7H_3O \,.\, COOH$.

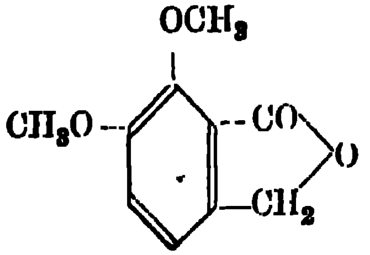
---

[1] Pictet and Finkelstein, *Ber.*, 1909, **42**, 1979; *C. R.*, 1909, **148**, 925.

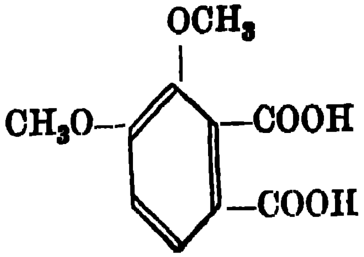
[2] Beckett and Wright, *Trans. Chem. Soc.*, 1875, **28**, 583.

[3] Matthiessen and Foster, *Annalen Suppl.*, I., 333; II., 378; V., 333.

IV. When heated with potash[1] it gives (by reduction) meconine, and (by oxidation) hemipinic acid—



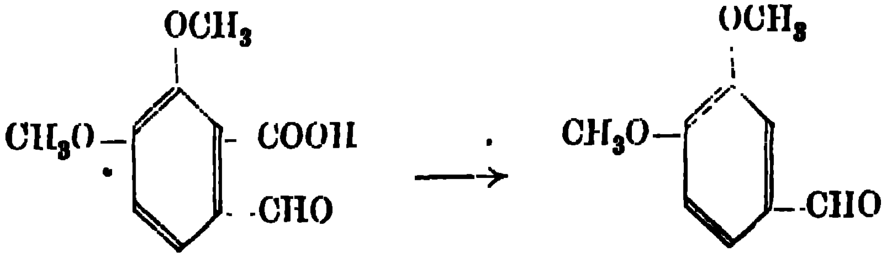
Meconine.



Hemipinic acid.

This last reaction is parallel to the formation of benzyl alcohol and benzoic acid by the action of potash upon benzaldehyde, so we must conclude that opianic acid contains an aldehydic group; and from the constitution of hemipinic acid it is obvious that this aldehyde radicle must be next the carboxyl group of opianic acid.

V. The final proof of the presence of an aldehyde group in opianic acid is furnished by the behaviour of its sodium salt when distilled with soda-lime.[2] Carbon dioxide is split off in the usual way, and the methyl ether of vanillin is left. The formula of opianic acid must therefore be that which is shown below—



Opianic acid. Methyl ether of vanillin.

5. *The Constitution of Cotarnine.*

The next stage in the proof of the narcotine constitution is reached through the constitution of cotarnine. This substance[3] is obtained along with opianic acid when narcotine is treated with oxidizing agents.

$$\underset{\text{Narcotine.}}{C_{22}H_{23}O_7N} + O + H_2O = \underset{\text{Opianic acid.}}{C_{10}H_{10}O_5} + \underset{\text{Cotarnine.}}{C_{12}H_{15}O_4N}$$

---

[1] Matthiessen and Foster, *Annalen Suppl.*, I., 332; II., 381.

[2] Beckett and Wright, *Trans. Chem. Soc.*, 1876, **28**, 583.

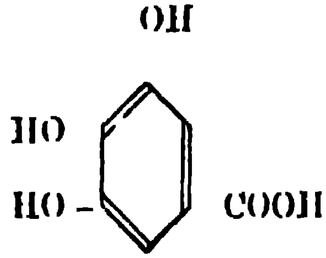
[3] Wöhler, *Annalen*, 1844, **50**, 1.

I. Cotarnine reacts with two molecules of methyl iodide, thus proving that it is a secondary base. The reaction product is called cotarnomethine methyl iodide,[1] and has the composition $C_{11}H_{11}O_4N(CH_3)_2I$.

II. By heating this body with caustic soda, trimethylamine is split off,[2] and cotarnone, $C_{11}H_{10}O_4$, remains. This proves to be an aldehyde, so that its formula can be written $C_{10}H_9O_3 . CHO$.

III. When cotarnone is oxidized with potassium permanganate[3] it gives a lactone, cotarnolactone, $C_{11}H_{10}O_6$, from which, on further oxidation, cotarnic acid, $C_{10}H_8O_7$, is obtained.

IV. By the usual reactions it is found that cotarnic acid[4] is dibasic, contains a methoxyl radicle, and has its carboxyl groups in the ortho-position to one another, as is shown by the ease with which it forms an anhydride. When heated with phosphorus and hydriodic acid to about 160° C. it yields gallic acid—



V. Now, gallic acid differs from cotarnic acid by the group $C_3H_2O_2$—

$$\underset{\text{Cotarnic acid.}}{C_{10}H_8O_7} - \underset{\text{Gallic acid.}}{C_7H_6O_5} = \underset{\text{From methoxy group}}{CH_2} + CO_2 + C$$

Part of this we can account for by the loss of carbon dioxide from a carboxyl group, since cotarnic acid is dibasic, while gallic acid is monobasic. We have thus one carbon atom left unaccounted for. This must be derived from the methylene group of a methylene ether We are in this way led to formulate cotarnic acid as a methyl-methylene-gallic-carboxylic acid, $C_6H(OCH_3)(CH_2O_2)(COOH)_2$. For such a substance there are only two possible formulæ—

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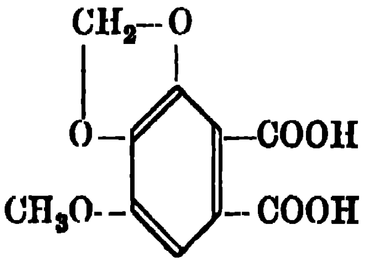
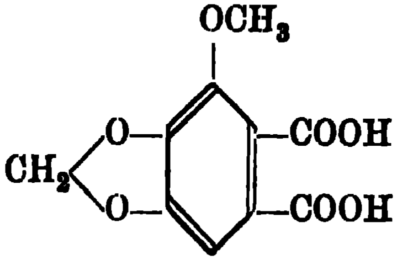
[1] Roser, *Annalen*, 1888, **249**, 157
[2] *Ibid.*, 141
[3] *Ibid.*, 168
[4] *Ibid.*, 163, 1899, **254**, 341.

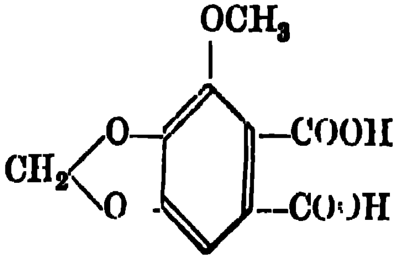


(I.)



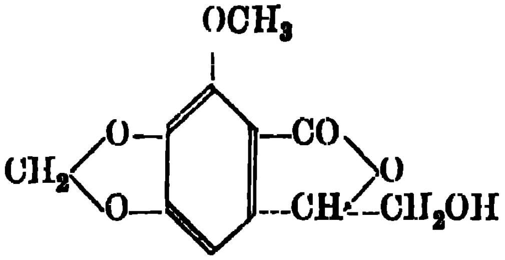
(II.)

Without going into details,[1] we may say that the general behaviour of the substance is best represented by (II.). Cotarnic acid therefore has the constitution—

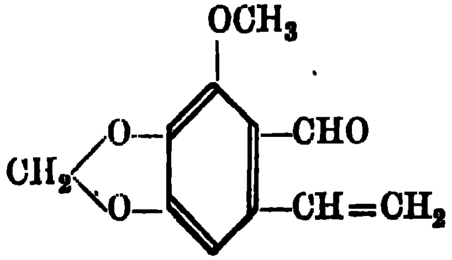


Cotarnic acid.

Cotarnolactone must therefore have the formula—



and cotarnone must be—



VII. But cotarnone was obtained from cotarnomethine methyl iodide and soda, whence cotarnomethine methyl iodide must have the structure—

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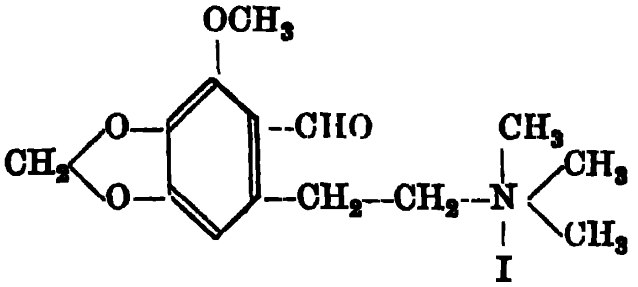
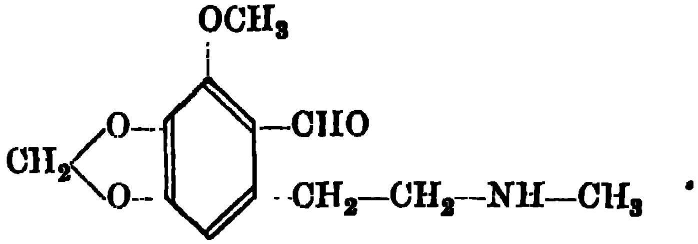
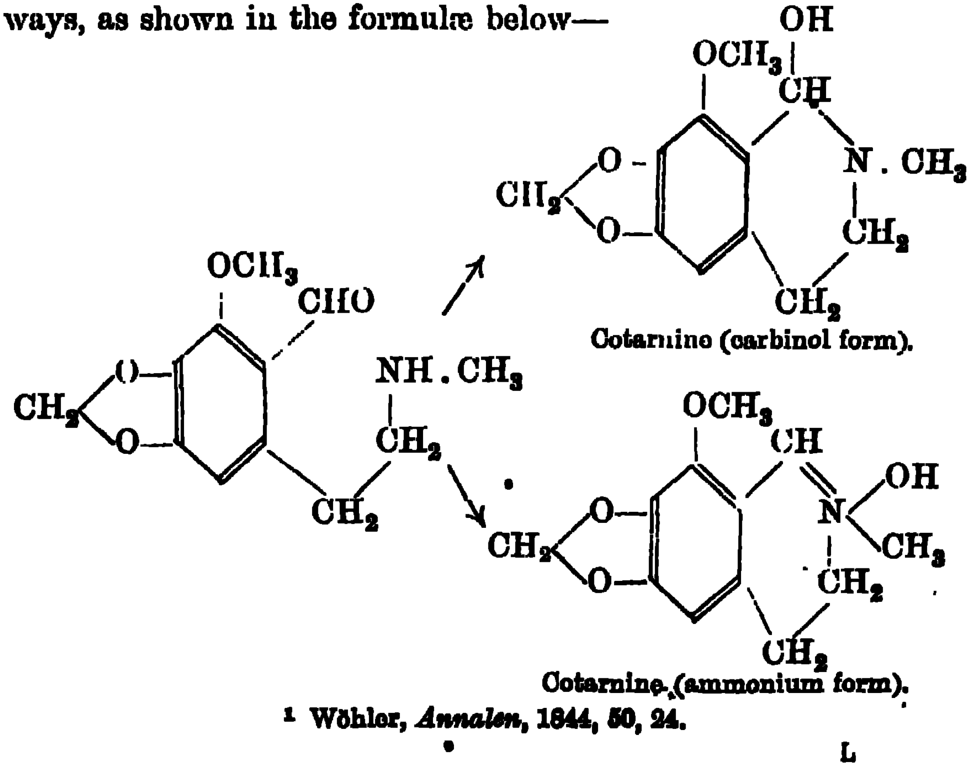
[1] Freund and Becker, *Ber.*, 1903, 36, 1521.



VIII. Hence cotarnine should have the following constitution, since cotarnomethine methyl iodide is obtained from it by the action of two molecules of methyl iodide:



IX. This formula, however, fails to explain the formation of a pyridine derivative, apophyllenic acid, when cotarnine is oxidized with nitric acid;[1] and to account for this we must assume that the free aldehydic group has disappeared in the course of some intramolecular ring-formation, which simultaneously brings into existence a pyridine chain within the molecule of cotarnine. This change we may represent in two ways, as shown in the formulæ below—



Cotarnine (carbinol form).

Cotarnine (ammonium form).

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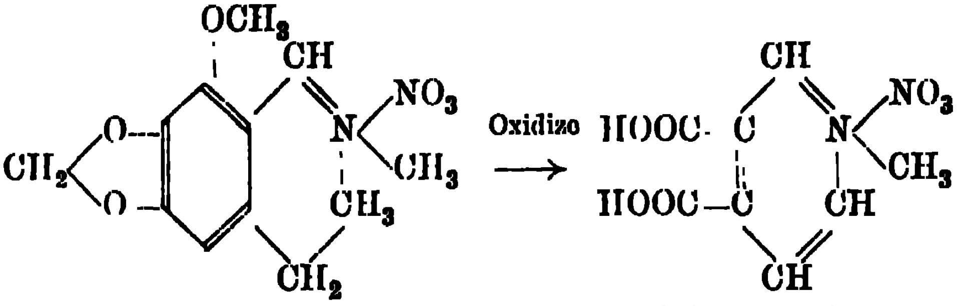
[1] Wöhler, *Annalen*, 1844, 50, 24.

It is generally agreed that the salts of cotarnine are best represented as derivatives of the ammonium form; for instance the production of apophyllenic acid can be made clear on this assumption—



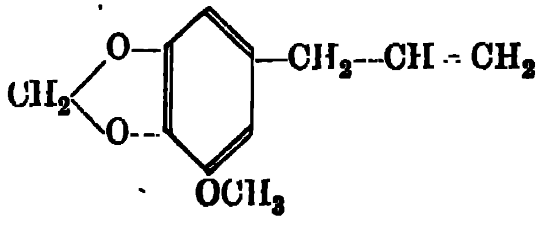
Cotarnine nitrate. Apophyllenic acid derivative.

With regard to the free base, however, the spectroscopic investigations of Dobbie, Lauder, and Tinkler[1] have shown that the structure varies with the solvent in which the substance is dissolved. In ether or chloroform the carbinol form is present; but the addition of alcohol to the solution brings into existence the ammonium form; in pure alcoholic solution no less than 25 per cent. of the substance is present as ammonium base.

6. *The Synthesis of Cotarnine.*

In the last section we dealt with the constitution of cotarnine, and we must now take up the synthesis of this substance. Synthetic cotarnine has been prepared by Salway;[2] but as the constitution of one of his intermediate products is left doubtful in the synthesis, it is not possible to establish the cotarnine structure from his work. In the light of the facts given in the last section, however, we can deduce the formulæ of the intermediate compounds.

I. The first stage in the process is the synthesis of β-3-methoxy-4 : 5-methylenedioxy-phenyl-propionic acid. Salway took as his starting-point the substance myristicin—



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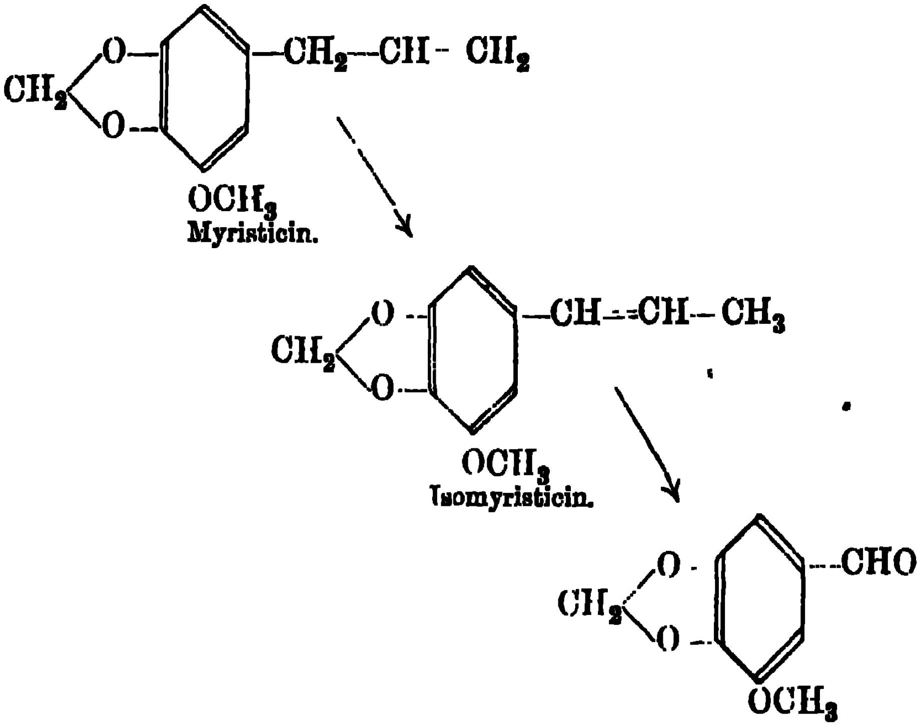
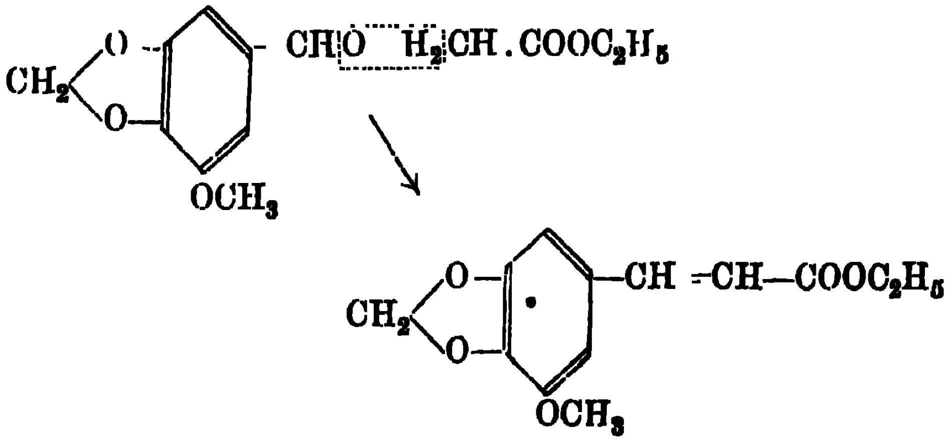
[1] Dobbie, Lauder, and Tinkler, *Trans. Chem. Soc.*, 1903, 83, 598

[2] Salway, *Trans. Chem. Soc.*, 1910, 97, 1208.

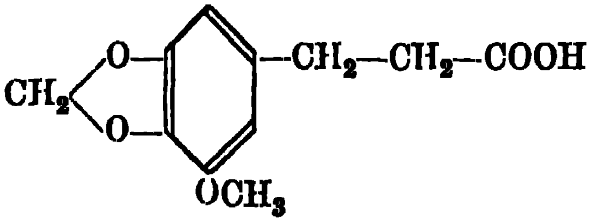
which he obtained from oil of nutmeg. This was heated with alcoholic potash to convert it into iso-myristicin; and the latter was then oxidized to myristicin aldehyde by means of potassium permanganate—



The aldehyde was then condensed with ethyl acetate by means of sodium, and the resulting ester was hydrolysed with alcoholic potash—



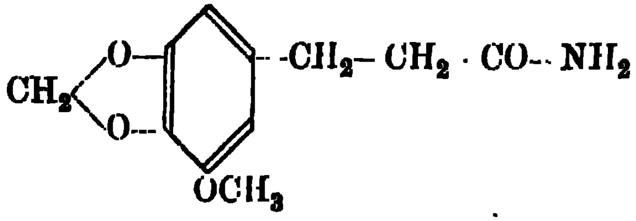
The substituted cinnamic acid thus produced was reduced with sodium amalgam, and in this way the required β-3-methoxy-4 : 5-methylenedioxy-phenyl-propionic acid was obtained.



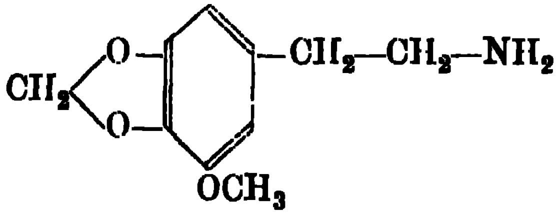
(I.)

II. The second stage ends in the production of phenylacetyl-β-3-methoxy-4 : 5-methylenedioxy-phenyl-ethylamine. The acid (I.) was converted into the amide (II.) in the usual way, and this in turn was changed into the corresponding amine (III.) by Hofmann's reaction—

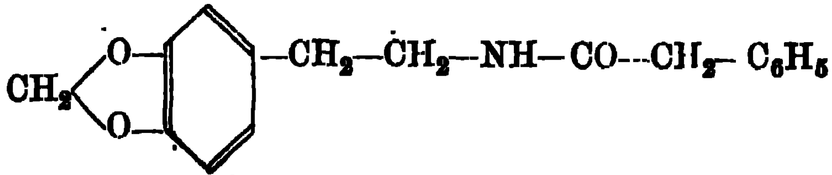
(II.)



(III.)



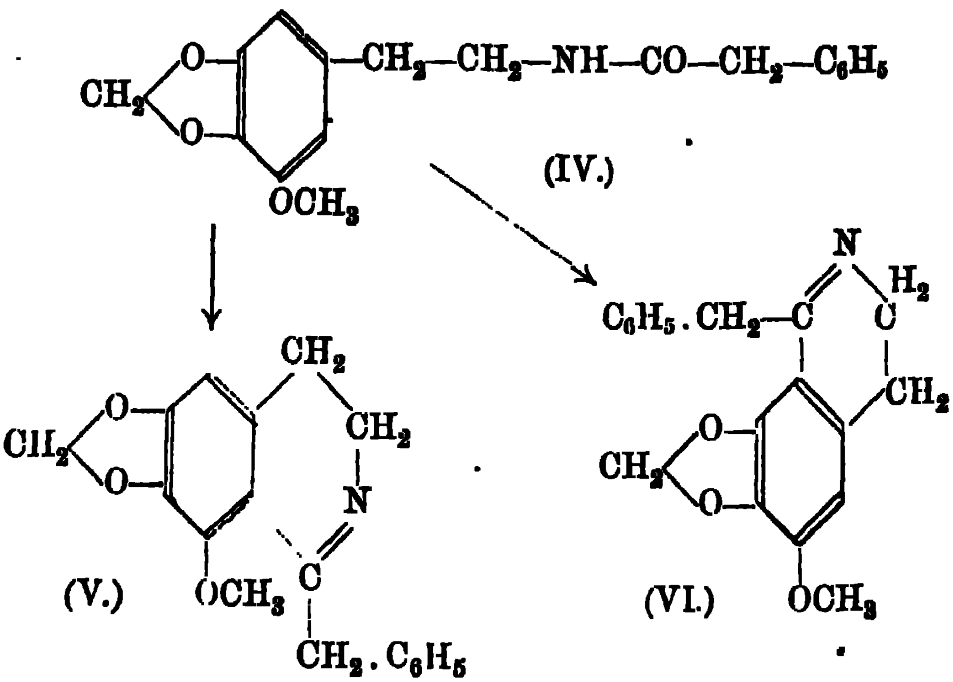
The phenylacetyl derivative (IV.) was then prepared by the ordinary method—



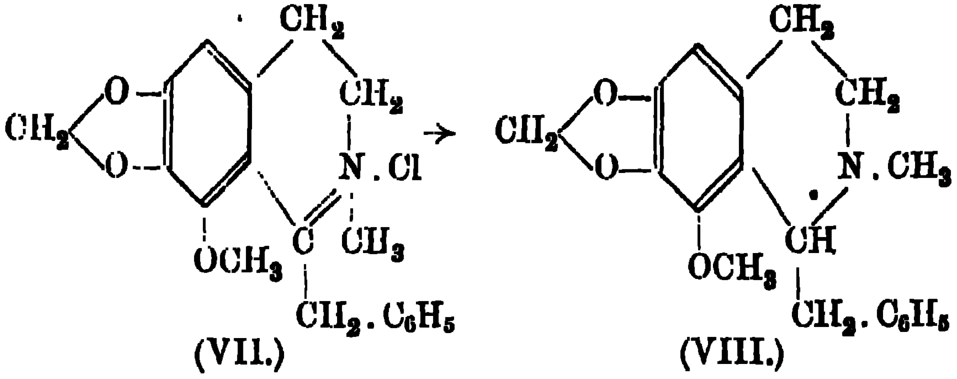
(IV.)

Phenylacetyl-β-3-methoxy-4 ; 5-methylenedioxy-phenyl-ethylamine.

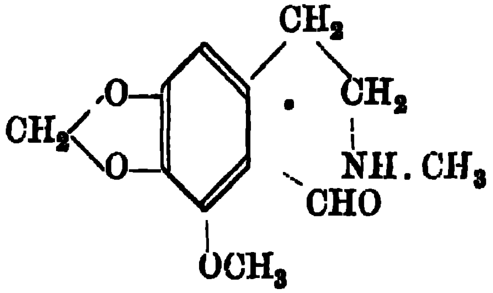
III. This phenylacetyl derivative was condensed by heating it with phosphoric oxide in presence of xylene; and in this way a mixture of two isomeric dihydro-isoquinoline derivatives was produced (V. and VI.).



IV. The substance (V.) is 8-methoxy-6 : 7-methylenedioxy-1-benzyl-3 : 4-dihydro-isoquinoline. To convert it into cotarnine, it is necessary in the first instance to form its metho-chloride (VII.), which is then reduced by means of tin and hydrochloric acid to 1-benzyl-hydrocotarnine (VIII.).



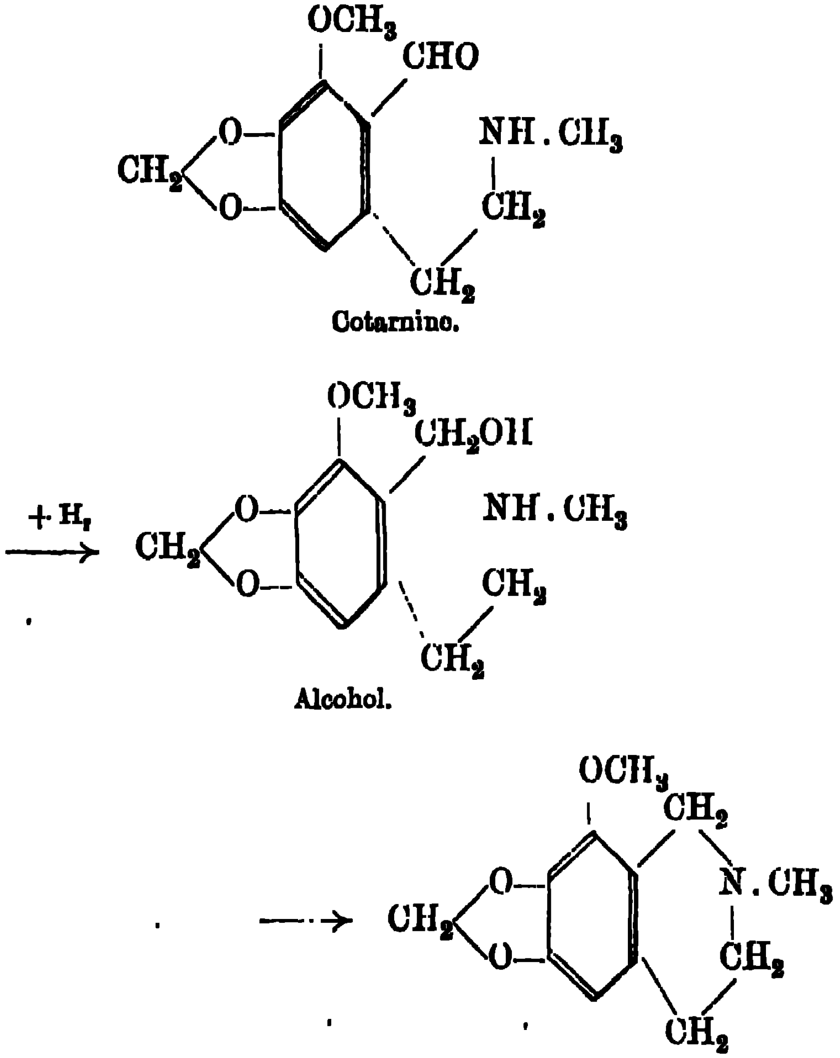
Finally, oxidation with manganese dioxide in presence of sulphuric acid converted the benzyl derivative into cotarnine—



It will be noticed that the substance (VI.), if treated in the same way as (V.), would give rise to an iso-cotarnine; and if the cotarnine constitution were unknown, this synthesis would throw no light upon the relative positions of the methoxy group and the pyridine ring.

7. *The Synthesis of Hydrocotarnine.*

On reduction, cotarnine is converted into hydrocotarnine,[1] which is formed in the manner indicated by the formulæ below—



Cotarnine.

Alcohol.

Hydrocotarnine.

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[1] Beckett and Wright, *Trans. Chem. Soc.*, 1875, 28, 577; Bandow and Wolffenstein, *Ber.*, 1898, 31, 1577.

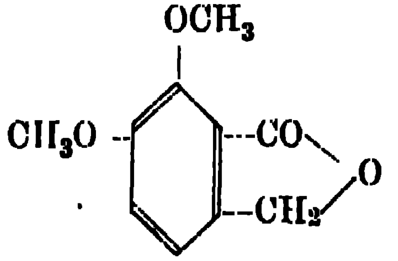
8. *The Constitution of Narcotine.*

We have now in the course of the previous sections amassed the material which we require in our consideration of the narcotine formula; and we may next proceed to deal with the question.

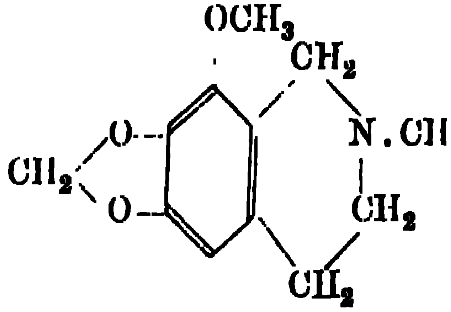
Narcotine contains no carboxyl or hydroxyl radicle. It is made up of one hydrocotarnine nucleus and one opianic acid nucleus, the latter being in the form of the lactone, meconine. This is shown by the action of reducing agents upon narcotine—

$$\underset{\text{Narcotine.}}{C_{22}H_{23}O_7N} + H_2 = \underset{\text{Meconine.}}{C_{10}H_{10}O_4} + \underset{\text{Hydrocotarnine.}}{C_{12}H_{15}O_3N}$$

We must now consider the mode of linkage of these two nuclei. When we examine the formulæ of meconine and hydrocotarnine—

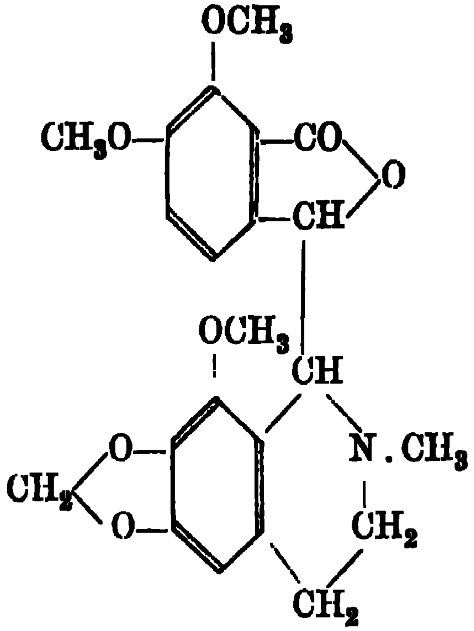


Meconine.



Hydrocotarnine.

it is obvious that the linking does not take place through an oxygen atom, as all of these are fully occupied. It must, therefore, occur by the conjunction of two carbon atoms, each of which loses a hydrogen atom in the union. The pair of atoms which are most likely to be concerned in the linkage are those which give rise to the aldehyde groups of opianic acid and cotarnine, so that the formula of narcotine would be written—



Narcotine.

9. *The Synthesis of Gnoscopine and Narcotine.*

Perkin and Robinson[1] showed that when cotarnine and meconine are boiled in alcoholic solution in presence of potassium carbonate the substance produced is identical with the alkaloid gnoscopine; and by fractionally crystallizing the *d*-bromocamphorsulphonate of the base[2] they were able to isolate the dextro and lævo forms of narcotine, gnoscopine being the racemic variety. The lævo-narcotine thus obtained was identical with the natural alkaloid.

10. *The Synthesis of Narceïne.*

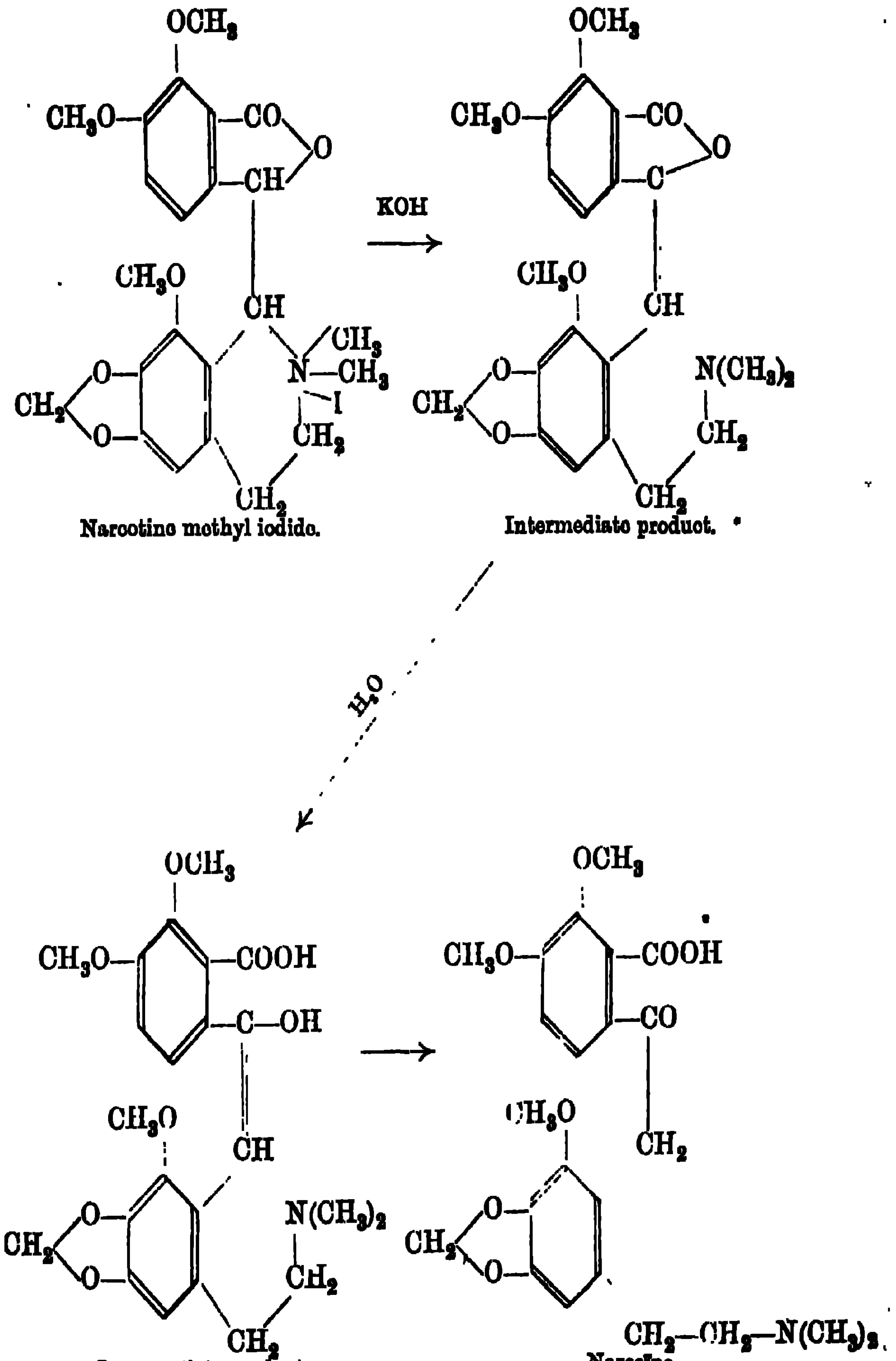
When the methyl iodide addition product of narcotine is treated with alkalis, it is converted into a substance narceïne, which was first called pseudo-narceine.[3] The course of the reaction may be formulated in the following way:—

---

[1] Perkin and Robinson, *Proc. Chem. Soc.*, 1910, **26**, 46.

[2] *Ibid.*, 131.

[3] Roser, *Annalen*, 1888, **247**, 167; 1889, **254**, 357; Freund and Frankforter, *ibid.*, 1893, **277**, 31.



Narcotine methyl iodide.

Intermediate product.

Intermediate product.

Narceine.

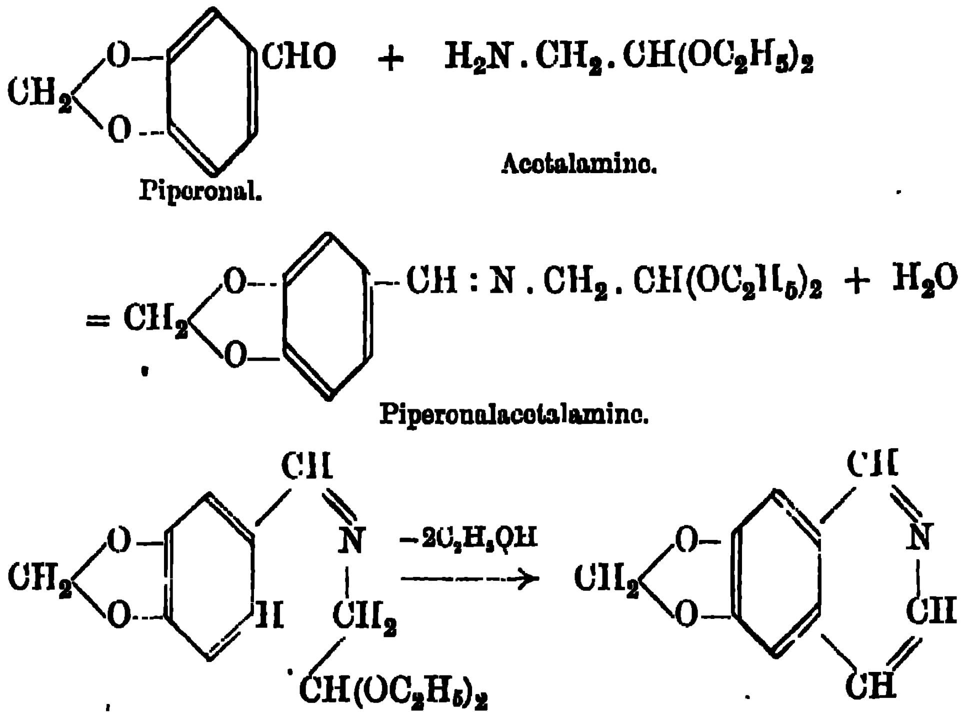
11. *The Synthesis of Hydrastinine.*

This substance, which occurs among the decomposition products of the alkaloid hydrastine, has been synthesized by Fritsch;[1] and as a knowledge of its constitution may help us in our consideration of the hydrastine formula, we may give a brief account of Fritsch's work before dealing with the natural alkaloid.

When chloracetal is treated with ammonia, it yields the substance acetalamine, which has the formula—

$$NH_2 . CH_2 . CH(OC_2H_5)_2$$

This substance can be made to condense with aromatic aldehydes; and when the products thus obtained are treated with sulphuric acid, alcohol is split off and isoquinoline derivatives are formed. If we apply this reaction to the case of piperonal, we shall have the following series of reactions:—



Piperonal.

Acetalamine.

Piperonalacetalamine.

Piperonalacetalamine.

Methylenedihydroxyisoquinoline.

When the methyl iodide addition product of this body is reduced by means of tin and hydrochloric acid, it gives the substance hydrohydrastinine—

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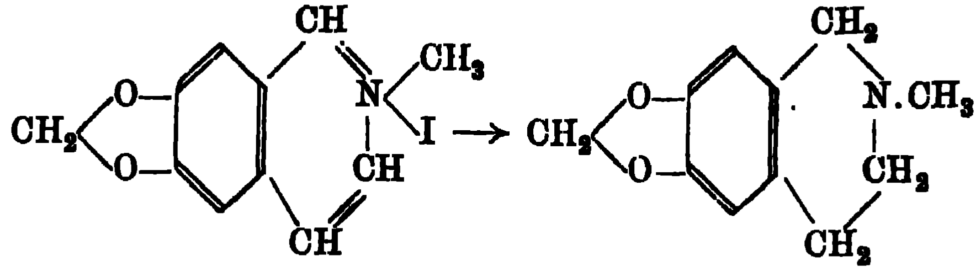
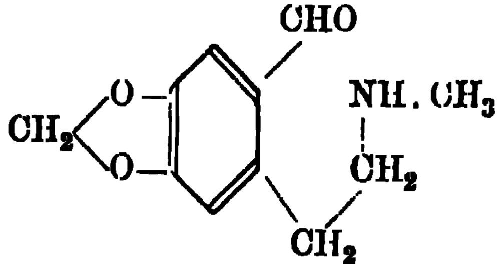
[1] Fritsch, *Annalen*, 1895, 286, 18.



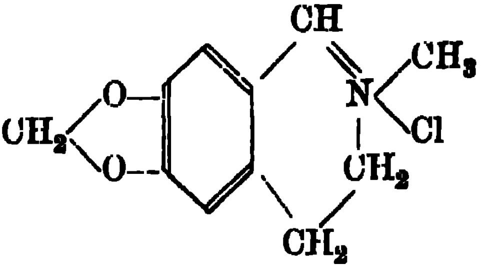
Iodomethylate. Hydrohydrastinine.

This last substance Freund[1] has converted into hydrastinine by oxidizing it with potassium bichromate and sulphuric acid.

Now, from the fact that the behaviour of hydrastinine, on reduction and salt formation, closely resembles that of cotarnine, we are enabled to put forward the following structural formula for it:—



Hydrastinine.



Hydrastinine hydrochloride.

This formula explains why hydrastinine behaves as an aldehyde, why it forms a ring-compound in presence of acids, why its salts contain one molecule of water less than the free base, why it yields apophyllenic acid on oxidation, and many other properties which the substance possesses. A comparison of their formulæ will show that cotarnine is a methoxylated hydrastinine.

12. *The Constitution of Hydrastine.*

Hydrastine contains one methoxyl group less than narcotine, but in all other respects it resembles that compound. Now, on oxidation with dilute nitric acid, hydrastine breaks down into hydrastinine and opianic acid just as narcotine breaks down into cotarnine and opianic acid. But, as was shown in the preceding section, cotarnine is methoxy-hydrastinine, so that we may conclude that if we eliminate the methoxy group from narcotine we shall have hydrastine. This actually proves to be the case; so that we may write the formula of hydrastine by simply taking that of narcotine and replacing the methoxyl radicle of the cotarnine half by a hydrogen atom. Hydrastine would therefore be—

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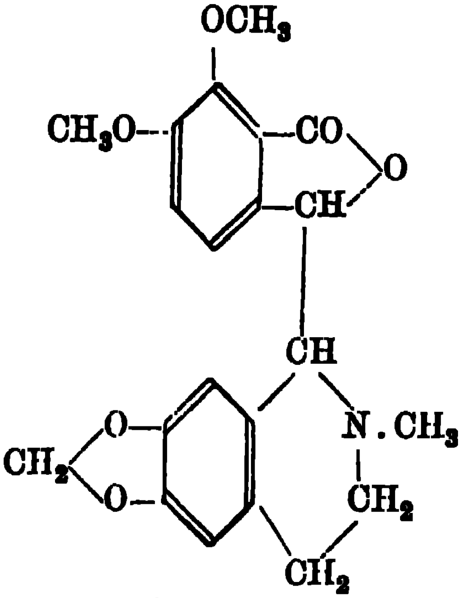
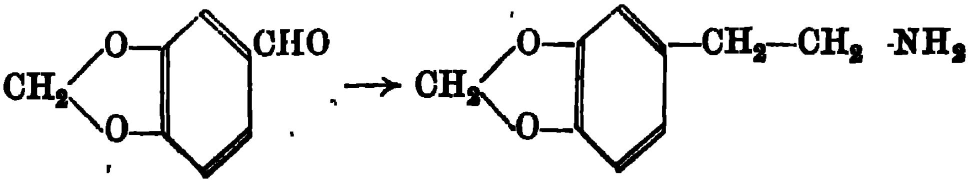
[1] Freund, *Ber.*, 1887, 20, 2403.



Hydrastine.

13. *The Synthesis of Berberine.*

Piperonal (I.) forms the starting-point of this series of reactions. When it is condensed with nitromethane in presence of sodium methylate, it produces piperonylidene-nitromethane from which in turn homopiperonaldoxime and homopiperonylamine (II.) are obtained by reduction[1]



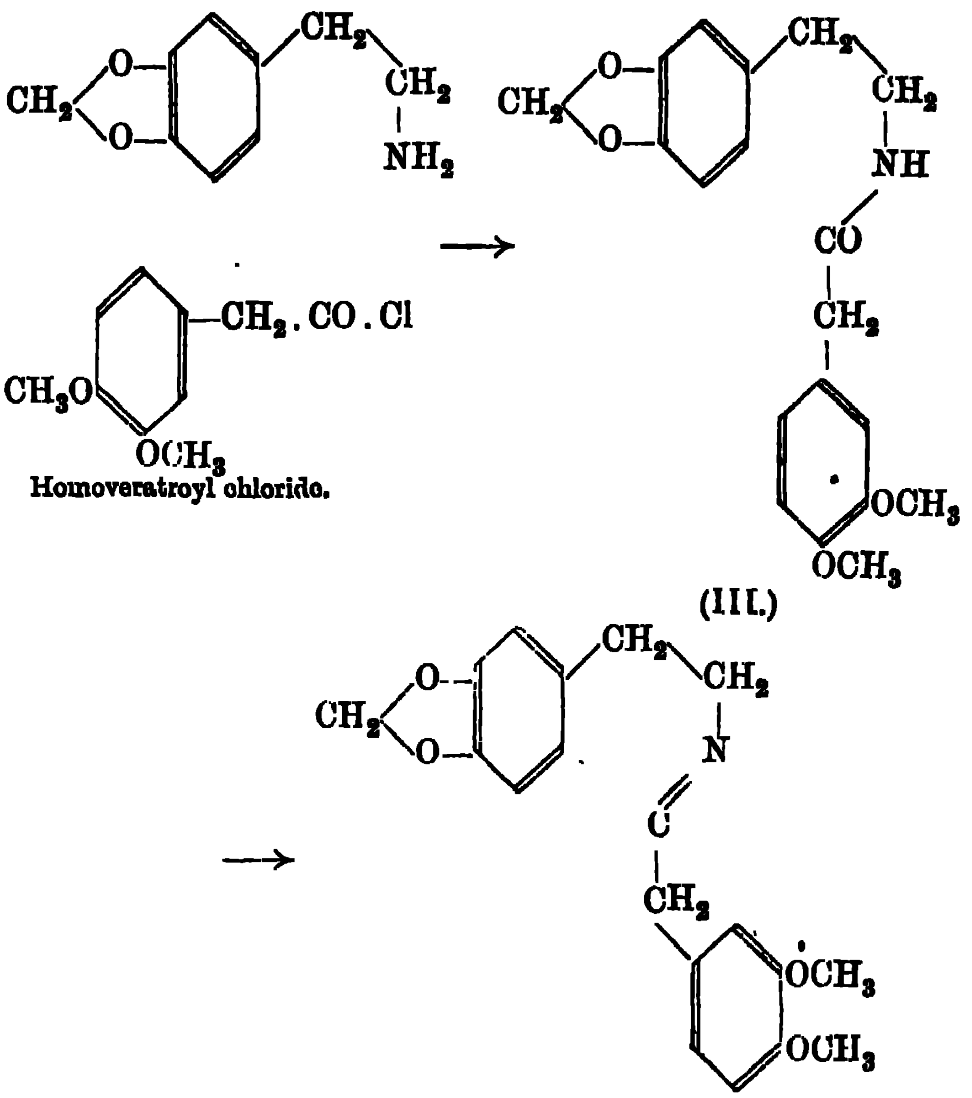
(I.) (II.)

Homoveratroyl chloride (the preparation of which has already been described[2]) is now allowed to act upon the amine yielding a condensation product (III.), which loses one molecule of water when heated with phosphorus pentoxide in xylene solution forming (IV.)—

---

[1] Bouveault and Wahl, *Compt. rend.*, 1902, **135**, 41; Medinger, *Monatsh.*, 1906, **27**, 237.

[2] See p. 138.



(III.)

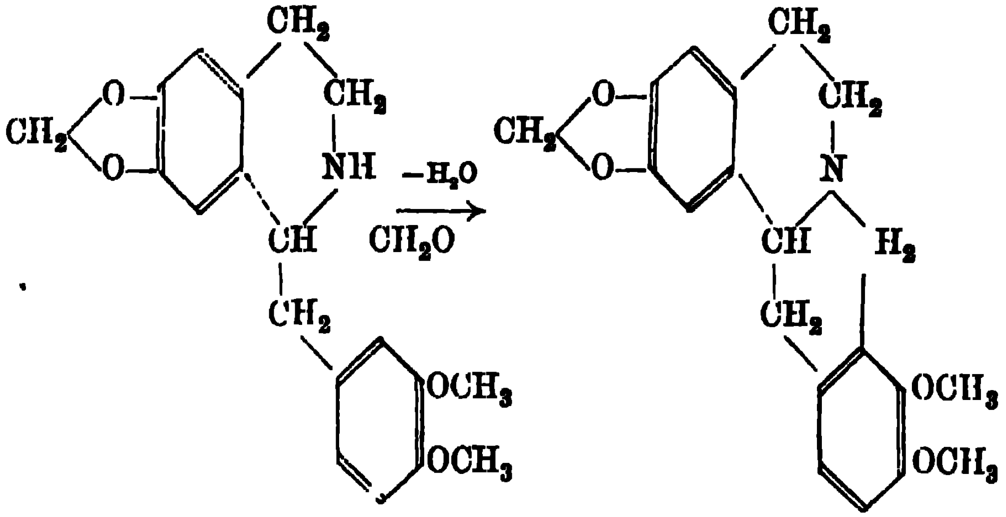
(IV.)

When the isoquinoline derivative (IV.) is reduced with tin and hydrochloric acid, it yields veratroyl-norhydrohydrastinine (V.). Condensation of the hydrochloride of this with methylal results in the entry of an extra carbon atom into the molecule, with the formation of a new six-membered ring. This produces tetrahydroberberine;[1] from which berberine itself is obtained by oxidation.[2]

---

[1] Pictet and Gams, *Compt. rend.*, 1911, 153, 386; *Ber.*, 1911, 44, 2480.

[2] Hlasiwetz and Gilm, *Annalen Supp.*, 1863, 2, 191.



(V.)

Tetrahydroberberine.

The true constitution of berberine is not yet agreed upon, as there are several ways in which hydrogen might be removed from tetrahydroberberine.

F. The Phenanthrene Group.

1. *The Relations between Morphine, Codeine and Thebaine.*

The general resemblance between morphine, codeine and thebaine can be seen by the comparison of their respective compositions:

$C_{17}H_{19}O_3N$	$C_{18}H_{21}O_3N$	$C_{19}H_{21}O_3N$
Morphine.	Codeine.	Thebaine.

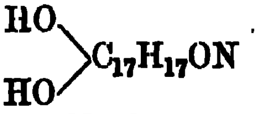
Morphine contains two hydroxyl groups, one of which is phenolic[1] and the other is an alcoholic radicle.[2] When morphine is methylated, codeine is formed, which has no phenolic properties. This establishes that codeine is methyl-morphine and carries its methyl radicle on the phenolic oxygen atom of morphine. The third oxygen atom in morphine and codeine is indifferent to reagents and is therefore assumed to be ethereal in character.[3] When subject to Zeisel's reaction, thebaine loses two methyl radicles; so that evidently it contains two methoxyl groups. The formulæ of the three substances may therefore be written as below:

---

[1] Matthiessen and Wright, *Proc. Roy. Soc.*, 1869, **17**, 364.

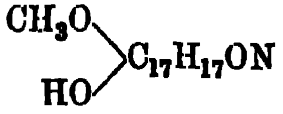
[2] Hesse, *Annalen*, 1884, **222**, 203.

[3] Vongerichten, *Annalen*, 1882, **210**, 105.



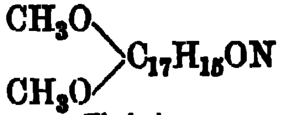
$$\left.\begin{array}{l}HO\\HO\end{array}\right\rangle C_{17}H_{17}ON$$

Morphine.



$$\left.\begin{array}{l}CH_3O\\HO\end{array}\right\rangle C_{17}H_{17}ON$$

Codeine.



$$\left.\begin{array}{l}CH_3O\\CH_3O\end{array}\right\rangle C_{17}H_{15}ON$$

Thebaine.

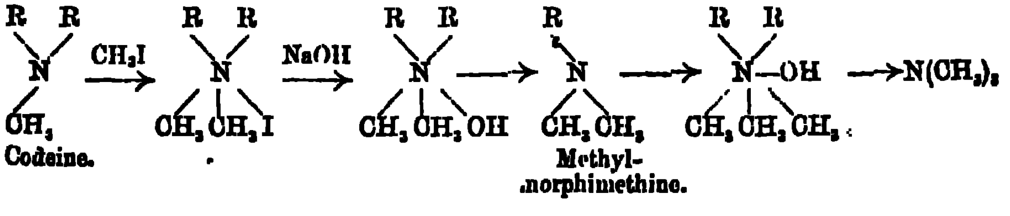
wherein the third oxygen atom is assumed to be ethereal in character.

All three alkaloids are tertiary bases and each of them contains a phenanthrene nucleus, as will be seen later.

2. *Methylmorphimethine.*[1]

I. Codeine unites directly with one molecule of methyl iodide, forming codeine-methyl-ammonium iodide. When this compound is boiled with caustic soda it yields a tertiary base, $C_{19}H_{23}O_3N$, which is known as methylmorphimethine. The process is evidently one of exhaustive methylation,* and the result proves that in codeine the nitrogen atom forms part of a ring.

II. When methyl iodide is allowed to unite with methylmorphimethine, a quaternary ammonium iodide is produced which can be converted into the corresponding methylmorphimethine-methyl-ammonium hydroxide in the usual way. On heating, this hydroxide decomposes and among the products trimethylamine is found. This proves that the nitrogen atom in methylmorphimethine-methyl-ammonium hydroxide is attached to three methyl radicles. Now since only one methyl group was introduced into the molecule in Stage I. and a second one in Stage II. it follows that the third methyl radicle must have been attached to the original nitrogen atom in codeine. Codeine, therefore, contains a nitrogen atom attached by two of its valencies to a cyclic grouping, whilst the third valency holds a methyl radicle. The course of the various reactions may be symbolised as follows, RR being used to represent the remainder of the codeine structure:



Codeine.

Methyl-morphimethine.

---

[1] Knorr, *Ber.*, 1889, **22**, 182.

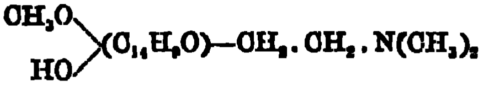
* See p. 120.

III. When treated with acetic anhydride,[1] methylmorphimethine yields hydroxy-ethyl-dimethylamine:

$$HO.CH_2.CH_2.N(CH_3)_2 .$$

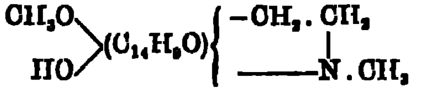
This chain might have been attached to the parent molecule either by the intermediation of the oxygen atom or of a carbon atom. By actual synthesis of the ether type of compound from the decomposition products,[2] it was proved that this structure was not the one sought; so that the side-chain is not attached to the rest of the codeine molecule by means of the oxygen atom. The linkage is therefore one between two carbon atoms; and the oxygen atom of hydroxy-ethyl-dimethylamine is not part of the original molecule, but is supposed to appear as the result of a reaction between water and the primary decomposition-product: a vinyl derivative.*

IV. Summarizing the information gained in the foregoing paragraphs, it is clear that methylmorphimethine may be represented by (1) while codeine corresponds to (2).



$$\left.\begin{matrix}CH_3O\\HO\end{matrix}\right>(C_{14}H_8O)—CH_2.CH_2.N(CH_3)_2$$

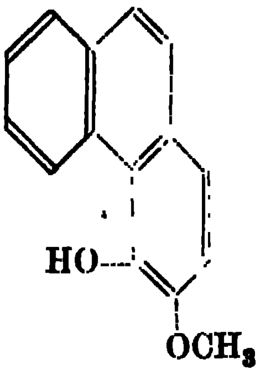
(1)



$$\left.\begin{matrix}CH_3O\\HO\end{matrix}\right>(C_{14}H_9O)\left\{\begin{matrix}-CH_2.CH_2\\ \qquad\quad |\\ \text{———}N.CH_3\end{matrix}\right.$$

(2)

V. The second product obtained when methylmorphimethine is decomposed with acetic anhydride is a methoxy-hydroxy-phenanthrene which has been shown, by synthesis[3] to have the structure:



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[1] Knorr, *Ber.*, 1889, **22**, 181, 1113; 1894, **27**, 1144; Knorr and Smiles, *ibid.*, 1902, **35**, 3009.

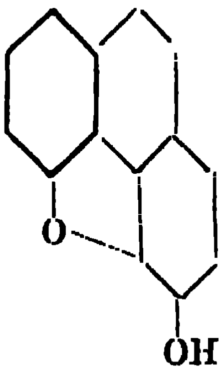
[2] *Ibid.*, 1905, **38**, 3143.

* The primary product is assumed to be $CH_2:CH.N(CH_3)_2$ which is then supposed to add on a molecule of water at the double bond.

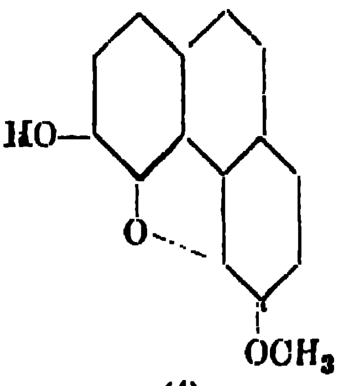
[3] Pschorr and Sumuleanu, *Ber.*, 1900, **33**, 1810, 1824; Pschorr and Vogtherr, *ibid.*, 1902, **35**, 4412.

3. *The Structures of Morphine and Codeine.*

I. The whole of the seventeen carbon atoms in the morphine molecule are now accounted for: since there are fourteen in the phenanthrene nucleus, two in the ring of which nitrogen forms a member and one in the methyl radicle attached to the nitrogen atom. The next step is to determine, if possible, the position of the ethereal oxygen atom in the molecule. Proof has been given above that this oxygen atom does not serve to link the nitrogen chain to the molecular nucleus; so it evidently must be linked with two carbon atoms of the phenanthrene group. Since a ring composed of four carbon and one oxygen atom is a fairly stable one, it is concluded that this grouping occurs in morphine; and this view is supported by evidence drawn from the effect of the Grignard reagent upon the analogous oxygen atom in thebaine.[1] Although the evidence is not perfect, it is generally accepted that morphine contains the skeleton shown in (3)—



(3)



(4)

II. The position of the remaining hydroxyl radicle has been determined in the following way. When codeine is oxidized by means of potassium permanganate or chromic acid,[2] it gives the corresponding ketone codeinone, the group —CH(OH)— being changed to a carbonyl radicle. On treatment with acetic anhydride,[3] codeinone yields 3-methoxy-4, 6-dihydroxy-phenanthrene, which places the hydroxyl group in position 6 as shown above in the formula (4).

---

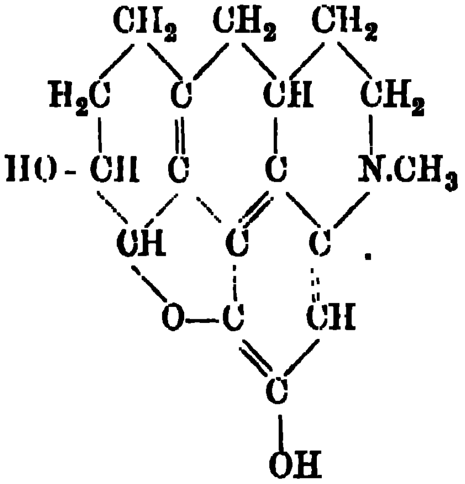
[1] Freund, *Ber.*, 1903, 36, 3234.

[2] Ach and Knorr, *Ber.*, 1903, 36, 3067.

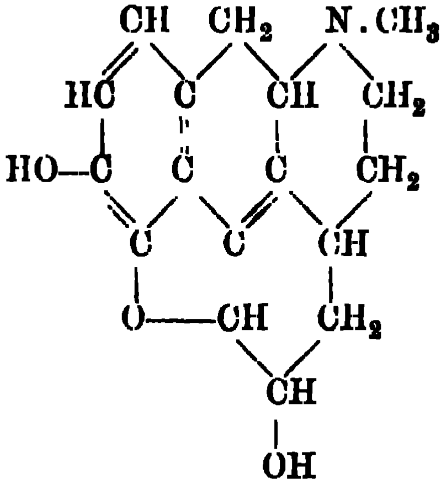
[3] Knorr, *Ber.*, 1903, 36, 3077.

III. It has now been shown that morphine contains a phenanthrene nucleus with six substituents attached to it: two places being occupied by the ends of the nitrogen ring, two by the hydroxyl groups and two by the ethereal oxygen. On counting the hydrogen atoms in this structure, it will be found that the total is six less than the number actually required by the formula for morphine. From this it is clear that morphine contains a partially reduced nucleus. The position of one of the reduced nuclei is indicated by the alcoholic hydroxyl in morphine; since this must be attached to a hexahydro-ring.

IV. The only remaining problem is the attachment of the nitrogen ring to the nucleus. There is no conclusive evidence on the point; and it will be sufficient to give here two of the formulæ suggested, one by Collie,[1] the other by Pschorr.*



Collie's formula.



Pschorr's formula.

Whatever formula be adopted for morphine, the corresponding codeine formula is obtained by substituting a methyl radicle for the hydrogen of the phenolic hydroxyl group.

It will be noticed that in each of the above morphine formulæ there are three asymmetric carbon atoms, from the presence of which it is reasonable to deduce that morphine will exist in two or more isomeric forms. In actual practice it is found that in addition to morphine itself there exist three isomeric bases: α-, β-, and γ-isomorphine; and in the case of codeine there are also three extra isomers: isocodeine, pseudocodeine and allopseudocodeine. Four isomeric methylmorphimethines[1] have also been found.

---

[1] Collie, private communication.

* This formula is based on Pschorr's formula for apomorphine (Pschorr, Jäckel and Fecht, *Ber.*, 1902, 35, 4379; Pschorr, Einbeck and Spangenberg, *ibid.*, 1907, 40, 1984, 1995, 1998.

The case of the codeines is sufficient to throw some light upon the problem. When phosphorus chloride acts upon codeine, the hydroxyl group of the alkaloid is replaced by a chlorine atom, yielding chlorocodide; but when this chlorocodide is reconverted into a hydroxyl derivative there is no regeneration of the original codeine, for any one of the three isomeric bodies may be produced according to the experimental conditions.[2]

Now when codeine and isocodeine are oxidized with chromic acid, they yield the same codeinone, which proves them to be structurally identical but stereoisomeric on account of the arrangement of the —CH(OH)— groups in space, a difference which vanishes when the secondary alcoholic radicle is oxidized to a carbonyl group. By the same test, pseudocodeine and allopseudocodeine are also two stereoisomers, but since the codeinone in this case is different from that derived from codeine itself, it is clear that structure isomerism must be taken into account in order to explain the difference between codeine and pseudocodeine. The correctness of this view seems to be established by the fact that pseudocodeinone, derived from pseudocodeine can be broken down to 3-methoxy-4, 8-dihydroxyphenanthrene; whereas codeine itself yields with the same treatment 3-methoxy-4, 6-dihydroxyphenanthrene. The isomerism of codeine and pseudocodeine therefore arises from the fact that the —CH(OH)— group occupies the position 6 in one molecule and the position 8 in the other.

These reactions enable us to compare the formulæ of Collie and Pschorr. The Collie formula agrees with the facts; whereas in the Pschorr formula the position 8 is already occupied by the isoquinoline ring. From this it is evident that Collie's formula is the more correct of the two.

Further evidence in favour of Collie's view and against Pschorr's formula is to be found in the following facts. When codeinone is treated with dilute hydrochloric acid it yields a secondary base thebenine; whereas when strong hydrochloric acid is employed, the tertiary base morphothebaine is produced. Both these substances are isomeric with codeinone. Now when each of these compounds is methylated two different trimethoxy-derivatives are formed, which, on oxidation, give rise to two different trimethoxy-carboxylic acids derived from phenanthrene:—

---

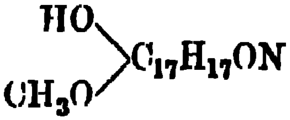
[1] Grimaux, *Compt. rend.*, **93**, 591; Hesse, *Annalen*, **222**, 223; Knorr, *Ber.*, 1894, **27**, 1144; Knorr and Smiles, *ibid.*, 1902, **35**, 3009; Schryver and Lees, *Trans.*, 1901, **79**, 1; Knorr and Hawthorne, *Ber.*, 1902, **35**, 3010.

[2] Schryver and Lees, *Trans.*, 1900, **77**, 1024; 1901, **79**, 563; 1907, **91**, 1408; Knorr and Hörlein, *Ber.*, 1906, **39**, 4409; 1907, **40**, 3844.

$$\begin{tikzcd}
\text{Morphothebaine} \arrow[d, "\text{Methylate and oxidize}"] & \text{Codeinone} \arrow[l, "\text{Conc. HCl}"'] \arrow[r, "\text{Dil. HCl}"] & \text{Thebenine} \arrow[d, "\text{Methylate and oxidize}"'] \\
\text{Phenanthrene-3, 4, 6-trimethoxy-carboxylic acid.} \arrow[d, phantom, "\text{Heat}"] & & \text{Phenanthrene-3, 4, 8-trimethoxy-carboxylic acid.} \arrow[d, phantom, "\text{Heat}"] \\
\text{3, 4, 6-trimethoxy-phenanthrene.} & & \text{3, 4, 8-trimethoxy-phenanthrene.}
\end{tikzcd}$$

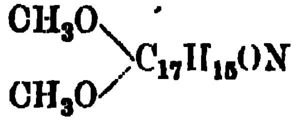
4. *Thebaine.*

An examination of the formulæ for codeine and thebaine



$$\left.\begin{matrix}HO\\CH_3O\end{matrix}\right>C_{17}H_{17}ON$$

Codeine.

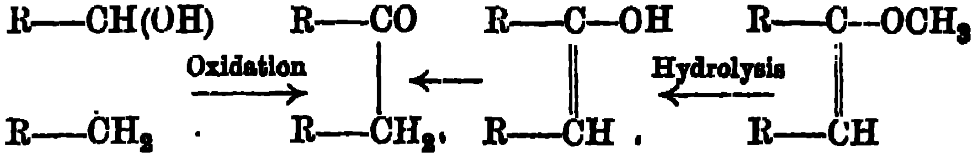


$$\left.\begin{matrix}CH_3O\\CH_3O\end{matrix}\right>C_{17}H_{15}ON$$

Thebaine.

will show that thebaine apparently contains a structure similar to codeine, except that it has two hydrogen atoms less in its nucleus. It is reasonable to assume that in thebaine there is a double bond which does not exist in the codeine molecule.

When thebaine is hydrolysed with dilute acid, it yields codeinone,[1] a ketone also derivable from codeine by oxidation. The most satisfactory explanation of these reactions is based on the assumption that thebaine is the ether derived from the enolic form of codeinone:—



Codeine. Codeinone. Enolic form. Thebaine.

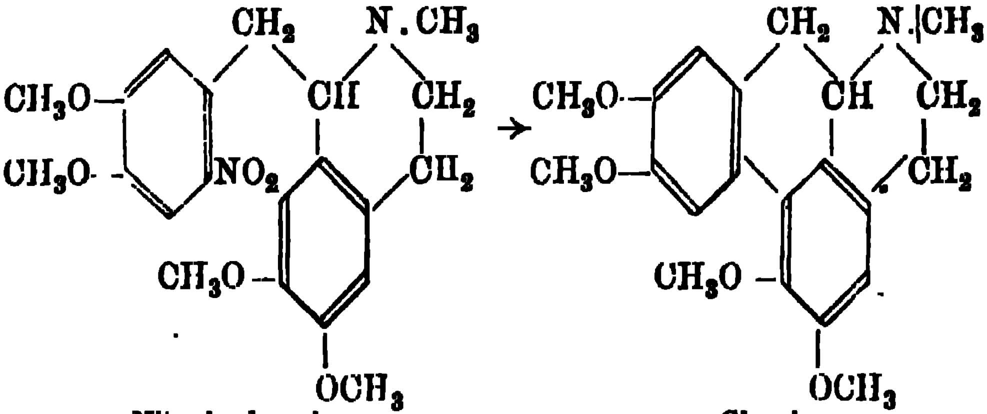
This view is in agreement with all the facts; and can be applied to either of the codeine formulæ given above.

---

[1] Knorr, *Ber.*, 1906, 39, 1409; Freund, *ibid.*, 844.

5. *Glaucine.*

The connection between the isoquinoline and the phenanthrene alkaloids is clearly brought out by the conversion of laudanosine into glaucine. Nitration of laudanosine produces nitro-laudanosine (I.) which is then reduced to amino-laudanosine. This last substance is then diazotized; and when the diazo-derivative is heated with copper powder, racemic glaucine (II.) is formed, which can be resolved into optical antipodes by means of tartaric acid.



Nitro-laudanosine.
(I.)

Glaucine.
(II.)

6. *The Relations between the Isoquinoline and Phenanthrene Alkaloids.*

There are certain similarities in the structures of the isoquinoline and phenanthrene alkaloids which are apt to be overlooked when the various substances are considered individually as we have done in the preceding pages; and it seems advisable to point out here some of the resemblances which can be detected.[*]

In the table on p. 167, some of the formulæ are collected together. In the first place, an examination of the structures of narceine, laudanosine and papaverine will show the step-by-step change from the open-chain grouping of the amino-chain in narceine to the closed and unsaturated pyridine ring in papaverine; and it will also reveal the identical distribution of the hydroxyl radicles in the three molecules, although the outward resemblance is masked to some extent by the substitution of a methylene ether radicle in narceine for the dimethoxyl grouping common to the others.

---

[*] I am indebted to Professor Collie for notes on this point.

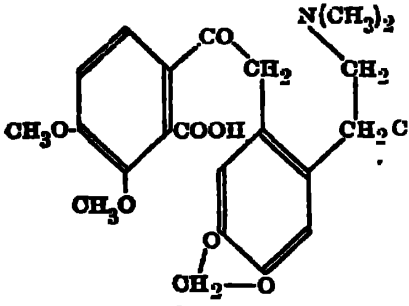
Comparison of narceine and hydrastine brings out the alliance between the two substances; for the carbonyl and carboxyl groups in the former compound become converted into the lactonic ring of hydrastine, at the same time as the open chain is contracted into the piperidine ring.

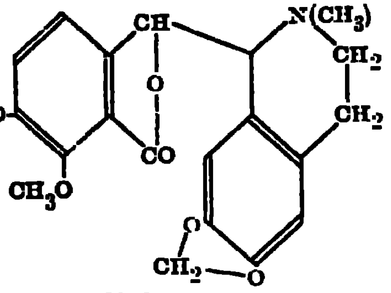
In the case of laudanosine, glaucine, thebaine and morphine, the main skeletons are obviously identical, and the change from the one formula to another is accomplished by a preliminary closing of a ring between two benzene nuclei, followed by a second ring-formation by elimination of water between two hydroxyl groups.

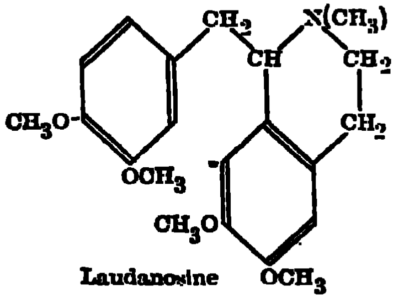
The inter-relations between papaverine, berberine and isocryptopine chloride can be seen by inspection of the formulæ on opposite page.

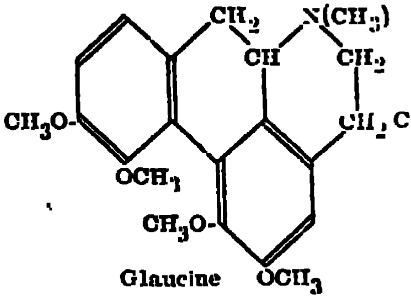
It has not been thought necessary to do more than give these examples, for the resemblances between other analogously-constituted alkaloids can easily be detected when attention has been drawn to the matter.

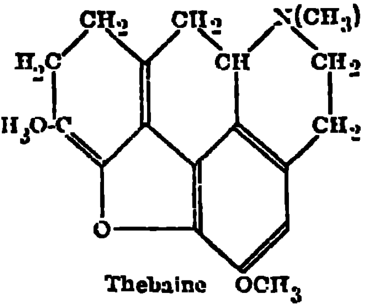
RELATIONS BETWEEN ISOQUINOLINE AND PHENANTHRENE ALKALOIDS.

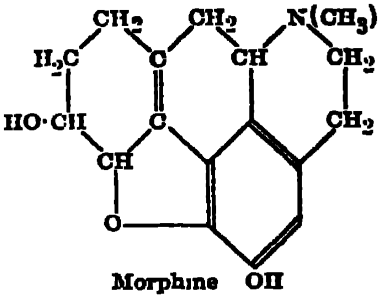

Narceine

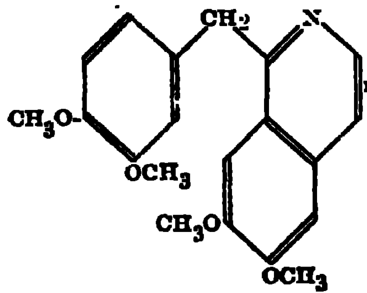

Hydrastine

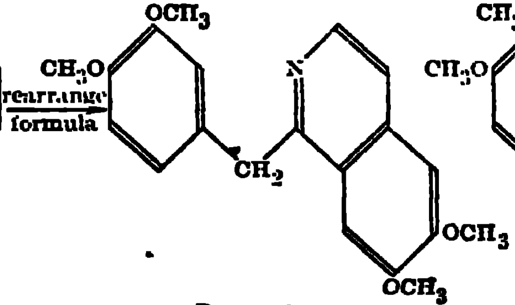

Laudanosine


Glaucine

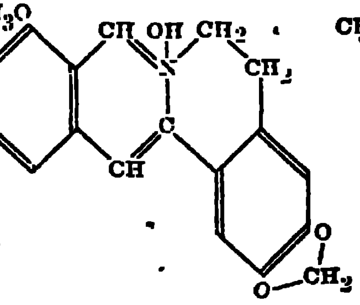

Thebaine

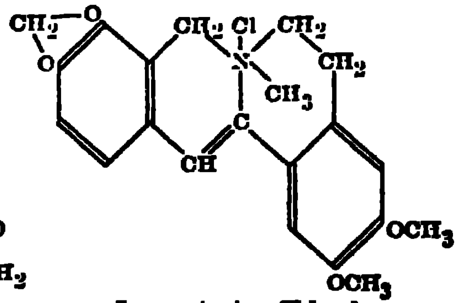

Morphine


Papaverine



Papaverine


Berberine


Isocryptopine Chloride

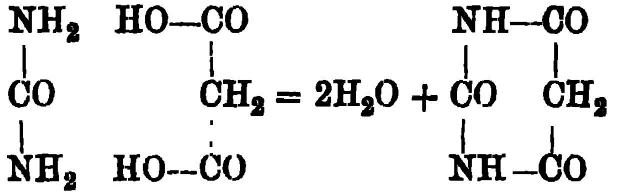
G.—THE PURINE * GROUP.

1. *The Synthesis of Uric Acid.*

The problem of the constitutions of the purine derivatives has proved one of the most complicated chapters in the history of modern organic chemistry; so complicated is it that we cannot devote space to any historical treatment of the matter, but must confine ourselves as closely as possible to the actual proofs of the constitutions of some of the purine series.

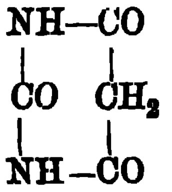
The most important member of the group is uric acid. This substance[1] has been synthesized in a variety of ways; but for the most part the syntheses throw no very clear light upon the constitution of the body. We may describe very briefly two of these synthetic methods of preparing uric acid, the first being due to Emil Fischer and the second to W. Traube.

When malonic acid is treated with urea, it yields a cyclic ureide, malonyl-urea or barbituric acid—

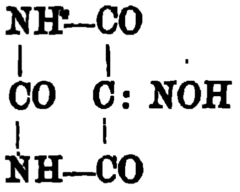


Barbituric acid.

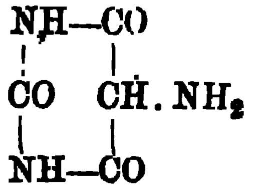
If barbituric acid be treated with nitrous acid, the methylene group is replaced by the isonitroso-radicle in the usual way, giving us, oximido-malonyl-urea, which is also called violuric acid; and on reduction of this substance the oximido group is converted into an amino-radicle, producing amino-malonyl-urea, or uramil—



Barbituric acid.



Violuric acid.



Uramil.

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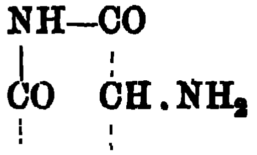
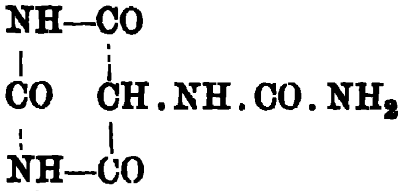
* This, like many other chemical terms, is what Lewis Carroll defined as a portmanteau word; it is derived from the two words *purum uricum*.

[1] Horbaczewski, *Monatsh.*, 1882, 3, 796; 1885, 6, 356; 1887, 8, 201, 584; Behrend and Roosen, *Ber.*, 1888, 21, 999; *Annalen*, 1889, 251, 235; Traube, *Ber.*, 1900, 33, 1371, 3035; Fischer and Ach, *Ber.*, 1895, 28, 2478; Fischer, *Ber.*, 1897, 30, 559.

On treatment with potassium cyanate, uramil takes up cyanic acid and is changed into pseudo-uric acid—

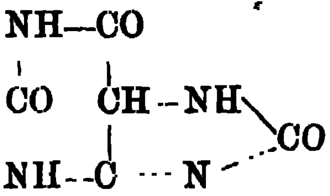


Uramil.

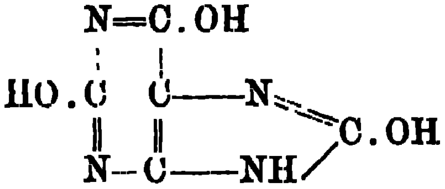


Pseudo-uric acid.

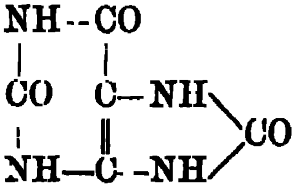
It is very hard to extract water from pseudo-uric acid, but this can be done by heating it with molten oxalic acid or by boiling it with hydrochloric acid. Under these circumstances one molecule of water is lost and uric acid is formed. Uric acid should therefore have the following constitution:—



Its property of forming salts could be ascribed to the existence of an enolic form, such as—

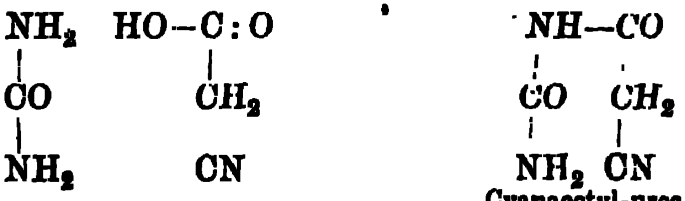


It is more usual, however, to consider uric acid to exist in the isomeric form—



Uric acid.

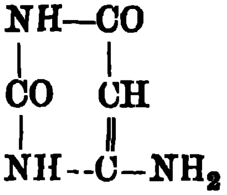
The second synthesis takes as its starting-point the condensation of urea with cyanacetic acid, which takes place under the influence of phosphorus oxychloride—



$$\begin{array}{lll} NH_2 & HO-C:O & \\ | & | & \\ CO & CH_2 & \\ | & & \\ NH_2 & CN & \end{array} \qquad \begin{array}{ll} NH-CO & \\ | & | \\ CO & CH_2 \\ | & | \\ NH_2 & CN \end{array}$$

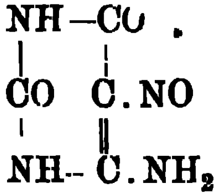
Cyanacetyl-urea.

Caustic soda causes cyanacetyl-urea to undergo an intramolecular change by which it is converted into amido-uracil—

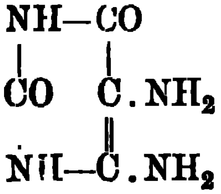


Amido-uracil.

When this is treated with nitrous acid it gives a nitroso compound which can be reduced with ammonium sulphide to diamido-uracil—

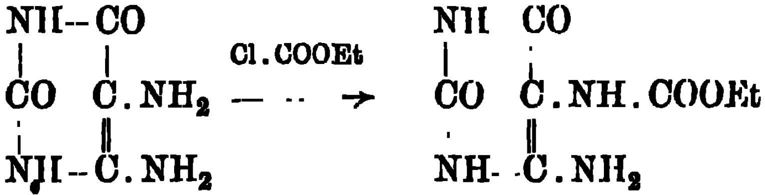


Nitroso compound.



Diamido-uracil.

The next step is to treat this diamido-derivative with caustic potash and chloroformic ester, by which means a urethane is formed—



Diamido-uracil.

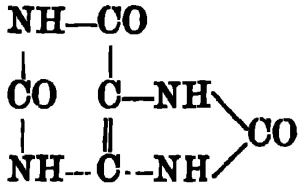
Diamido-uracil urethane.

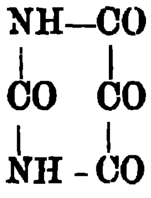
By heating the sodium salt of this substance to 180°–190° C. the sodium salt of uric acid is obtained.

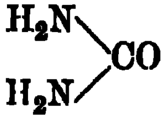
By adapting this last synthesis we can obtain many uric acid derivatives; for we may use substituted ureas instead of the parent substance, or we may replace the urea by guanidine, or, lastly, we may discard the chloroformic ester in favour of formic ester.

Before leaving the question of uric acid we must glance for a moment at the behaviour of that substance when treated with various oxidizing agents.

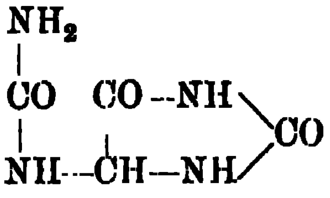
When the oxidation is carried out by means of cold nitric acid, the six-membered ring of uric acid remains intact, while urea is split off. The oxidized ring which remains can be derived from mesoxalic acid and urea; it is termed alloxan, or mesoxalyl-urea—


Uric acid.

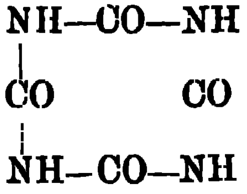

Alloxan.


Urea.

If, on the other hand, we use alkaline potassium permanganate solution as our oxidizing agent, the five-membered ring remains unbroken, while the six-membered one is destroyed. The first products in this case are two substances, uroxanic acid, $C_5H_8N_4O_6$, and oxonic acid, $C_4H_5N_3O_4$, which are further oxidized to allantoin—

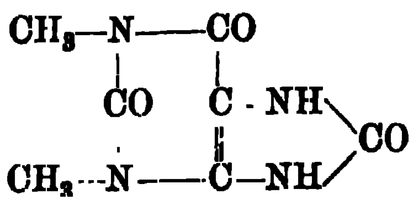

Allantoin.

With hydrogen peroxide the sodium salt of uric acid yields a substance of the formula $C_4H_4N_4O_4$, tetracarbonimide, which acts as a weak tetra-basic acid; on this account the following formula has been tentatively ascribed to it:—

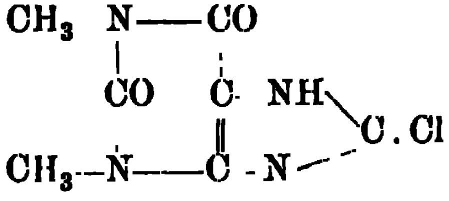


2. *The Synthesis of Theophylline.*

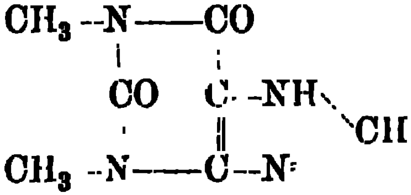
If in the uric acid syntheses we substitute symmetrical dimethyl-urea for the parent substance, we obtain in the end dimethyl-uric acid—



When this is treated with trichloride and oxychloride of phosphorus at 150° C. it is converted into a substance chlorotheophyllin, one atom of chlorine replacing a hydroxyl group. Chlorotheophylline must, therefore, have the following constitution:



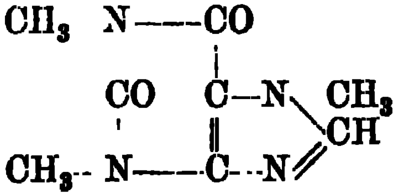
By reducing with hydriodic acid, theophylline[1] is formed—



Theophylline.

3. *The Synthesis of Caffeine.*

Caffeine[2] is obtained by the action of methyl iodide upon theophylline. Its constitution is therefore expressed by—



Caffeine.

4. *The Synthesis of Theobromine.*

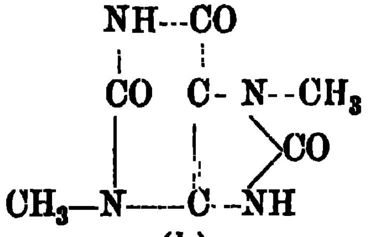
If we take as a starting-point the dimethyl-uric acid which has the constitution (I.) shown below, and treat it with phosphorus oxychloride, we shall find that it gives chlorotheobromine (II.), which, on reduction with hydriodic acid, yields theobromine (III.).[3] The reactions are parallel to those which lead from the isomeric dimethyl-uric acid to theophylline—

---

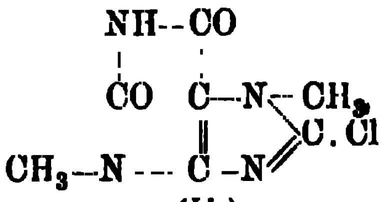
[1] Fischer and Ach, *Ber.*, 1895, 28, 3135.

[2] *Ibid.*

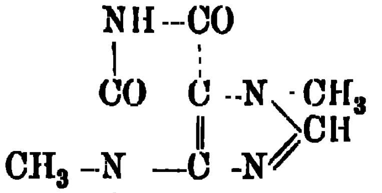
[3] Fischer, *Ber.*, 1897, 30, 1889.



(I.)



(II.)

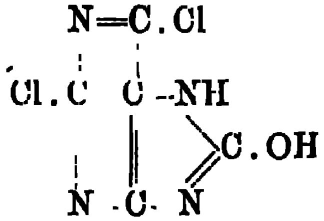


Theobromine.

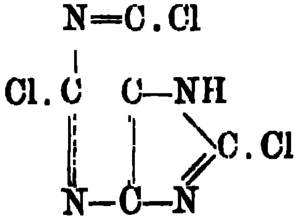
(III.)

5. *The Synthesis of Purine.*

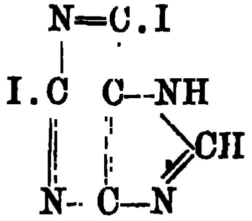
When the sodium salt of uric acid is treated with oxychloride of phosphorus it yields a hydroxy-dichloro-purine of the following formula:—



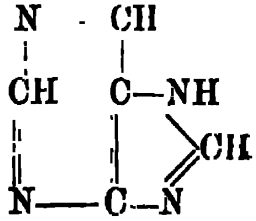
This, by means of trichloride of phosphorus, can be changed into a trichloro-derivative, the third hydroxyl group being replaced by a chlorine atom. The substance thus formed, trichloropurine, is then treated with hydriodic acid at 0° C., whereby di-iodopurine is produced. This, by reduction with water and zinc dust, gives purine itself—



Trichloropurine.

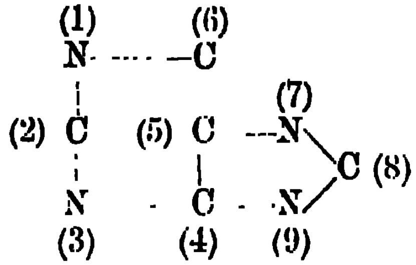


Di-iodopurine.



Purine.

Purine is the substance to which all the substances of the purine group are usually referred; the derivatives being distinguished by means of the system of numbering shown in the following scheme:—

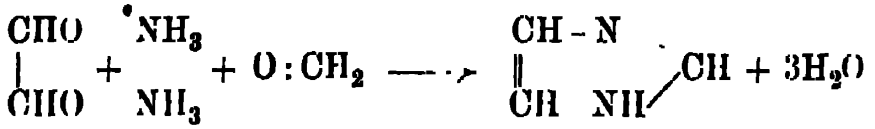


According to this, the substance xanthine is 2, 6-dihydroxy-purine; theophylline would be 1, 3-dimethyl-xanthine; caffeine would be 1, 3, 7-trimethyl-xanthine; theobromine would be 3, 7-dimethyl-xanthine; and uric acid 8-hydroxy-xanthine.

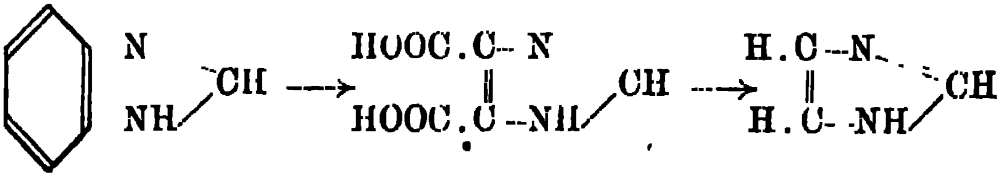
II.—The Glyoxaline Group.

In recent years a fresh nucleus, glyoxaline, has been detected among the basal substances of some of the alkaloids. Glyoxaline itself is metameric with pyrazole: and it may be regarded as a pyrrol nucleus wherein one of the methine radicles is replaced by a nitrogen atom.

The parent substance of the glyoxaline group may be obtained by condensing together glyoxal, ammonia, and formaldehyde:—



It may also be produced by oxidizing benzimidazole with permanganate and then heating the dicarboxylic acid so formed—



An examination of the purine structure will show that it may be regarded as containing a glyoxaline ring condensed with a pyrimidine nucleus; so that the purine derivatives may be considered as partly derived from glyoxaline: but it is not necessary to lay too much stress upon this relationship since the uric acid group is sufficiently distinct to permit of its being regarded as a class by itself.

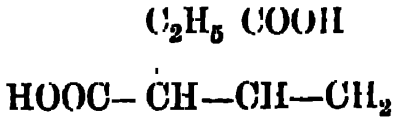
1. *The Constitution of Pilocarpine.*

Pilocarpine occurs in jaborandi leaves in conjunction with several related alkaloids: pilocarpidine,[1] isopilocarpine,[2] pilosine,[3] ψ-pilocarpine,[4] and ψ-jaborine.[*] The general structure of pilocarpine has been established in the following manner:—

The composition of pilocarpine is $C_{11}H_{12}N_2O_2$. Although it contains two nitrogen atoms it does not yield an amide with acetyl chloride; so it is clear that both nitrogen atoms must be tertiary ones. Oxidation[5] with permanganate produces from pilocarpine a mixture of methyl-urea, homopilopic acid, and pilopic acid. As pilopic acid is derived from homopilopic acid by further oxidation, it will be best to examine first the constitution of homopilopic acid.

Homopilopic acid is a lactonic acid, containing one lactone ring and one free carboxyl radicle. From the stability of the lactonic structure, the substance is evidently a γ-lactone. Its composition is $C_8H_{12}O_4$.

When fused with caustic potash, homopilopic acid gives α-ethyltricarballylic acid:—



$$HOOC-\overset{C_2H_5}{CH}-\overset{COOH}{CH}-CH_2\cdot COOH$$

This substance must arise from a hydroxy-acid by the action of the potash; and for this hydroxy-acid three formulæ are possible, from which we must select the correct one:—

---

[1] Harnack, *Annalen*, 1887, **238**, 230.

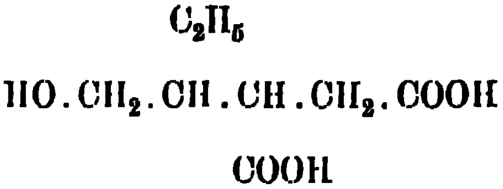
[2] Petit and Polonowsky, *J. Pharm. Chim.* (vi.), 1897, **5**, 370, 430; **6**, 8.

[3] Pyman, *Proc.*, 1912, **28**, 267.

[4] Petit and Polonowsky, *Chem. Zentr.*, 1897 (i), 1126.

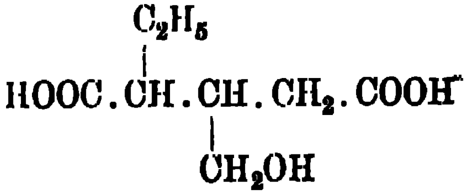
[*] The supposed alkaloid jaborine appears to be a mixture (Jowett, *Trans.*, 1900, **77**, 474, 851; 1901, **79**, 581, 1381).

[5] Jowett, *Trans.*, 1900, **77**, 474, 851; 1901, **79**, 581, 1381; compare Pinner, *Ber.*, 1900, **33**, 1424, 2537; 1901, **34**, 727; 1902, **35**, 204, 2443; 1905, **38**, 1510.



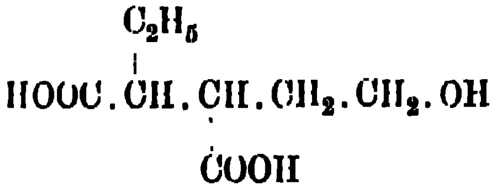
$$HO.CH_2.\overset{C_2H_5}{CH}.\underset{COOH}{CH}.CH_2.COOH$$

(I.)



$$HOOC.\overset{C_2H_5}{\overset{|}{CH}}.\underset{CH_2OH}{\underset{|}{CH}}.CH_2.COOH$$

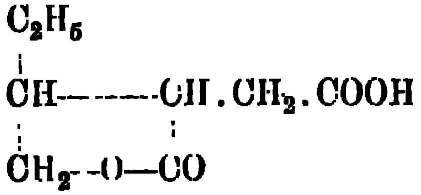
(II.)



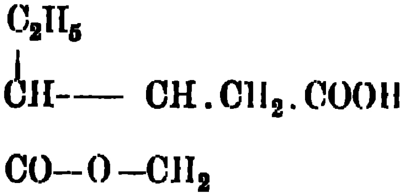
$$HOOC.\overset{C_2H_5}{\overset{|}{CH}}.\underset{COOH}{CH}.CH_2.CH_2.OH$$

(III.)

Now pilopic acid appears to be derived from homopilopic acid by loss of carbon dioxide and oxidation of the carbon atom which carried the destroyed carboxyl radicle. Of all the possible γ-lactonic formulæ derived from the three acids shown above, only two can fulfil this condition—

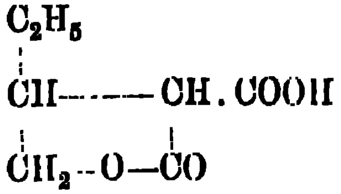


(A)

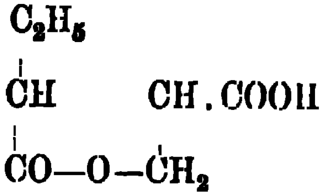


(B)

The corresponding formulæ for pilopic acid would therefore be—



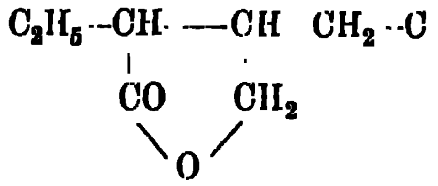
(a)



(b)

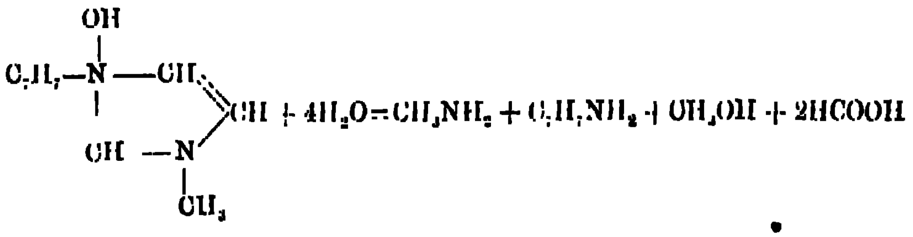
Now, owing to the fact that in (a) there are two carboxyl radicles (one in lactone form) attached to the same carbon atom, we should expect such a compound to lose carbon dioxide easily on heating as malonic acid does. Pilopic acid, however, is stable even at 200° C. It seems most probable, therefore, that pilopic acid has the formula (b); which leads us to the formula (B) for homopilopic acid.

By this reasoning, pilocarpine itself must contain the skeleton

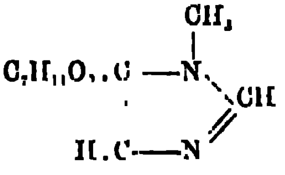


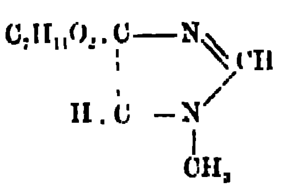
in addition to a group $C_3H_5N_2$, which disappears completely on oxidation. With regard to the structure of this last complex we must look for further evidence.

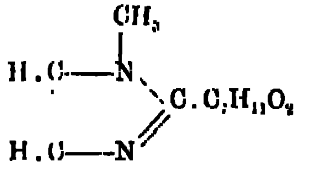
When derivatives of glyoxaline are allowed to interact with alkyl halides, ammonium compounds are formed which break down under the action of caustic potash, yielding primary amines. Now when pilocarpine is submitted to this series of reactions, it gives rise to equimolecular quantities of methylamine, methyl alcohol, and $C_7H_7.NH_2$, plus two-molecular proportions of formic acid. This decomposition can be accounted for by assuming that its methyl iodide addition product is transformed by caustic potash into an ammonium hydroxide of the following structure:—



Thus pilocarpine itself may have one of the following structures:—*







The exact constitution of pilocarpine is not yet defined; but as far as the evidence at our disposal is concerned either the formula proposed by Pinner and Schwarz[1] or that suggested by Jowett[2] suffices to account for the reactions of the compound—

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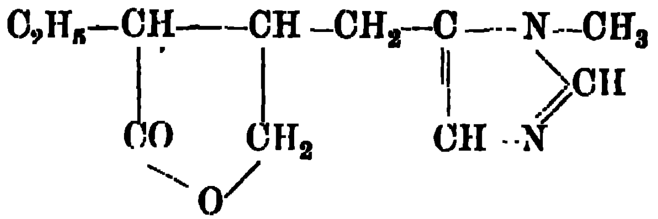
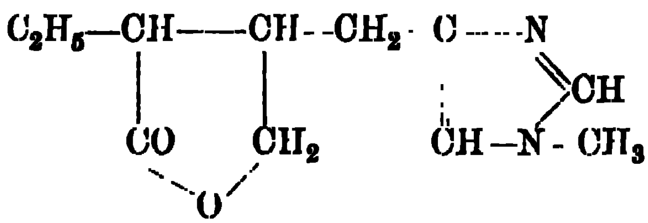
* It is assumed that the union between the glyoxaline group and the rest of the molecule is originally through carbon, a wandering of the homopilopic group taking place to the nitrogen during the decomposition.



Pinner's formula.



Jowett's formula.

2. *Isopilocarpine and Pilosine.*

The oxidation of pilocarpine and isopilocarpine gives rise to the same products; which shows that the two substances are closely allied in structure. Their chemical properties are also very similar; and the absorption spectra of their nitrates are identical.[3] Further, pilocarpine and isopilocarpine, when treated with alcoholic potash, are both converted into an equilibrium mixture containing chiefly isopilocarpine. From evidence of this kind, Jowett[4] regards isopilocarpine as a stereoisomer of pilocarpine; and this view appears to cover all the more important reactions of the alkaloids.

The constitution of pilosine has been investigated by Pyman.[5] He finds that on distillation with potash solution it yields benzaldehyde and a substance called pilosinine, which closely resembles pilocarpine in physiological action. He ascribes to the two substances the following structures:—

---

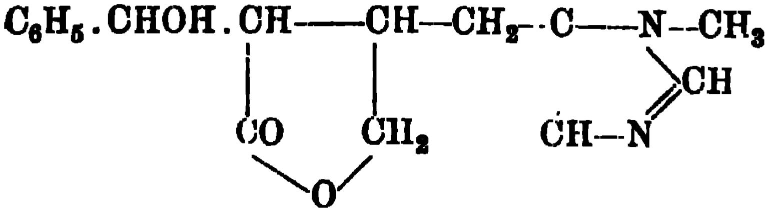
[1] Pinner and Schwarz, *Ber.*, 1902. 35, 2441; Pinner, *ibid.*, 1905, 38, 1510.

[2] Jowett. *Trans.*, 1903, 83, 442; 1905, 87, 794; Pyman, *Trans.*, 1910, 97, 1814.

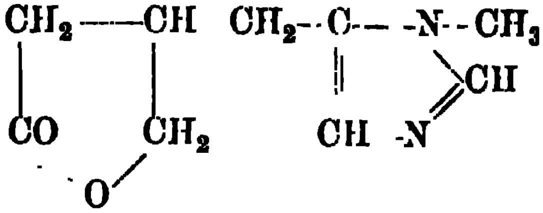
[3] Dobbie, *cf.* Hartley, *Proc. Chem. Soc.*, 1903, 19, 122.

[4] Jowett, *Trans.*, 1903, 83, 438; 1905, 87, 794.

[5] Pyman, *Proc.*, 1912, 28, 267.



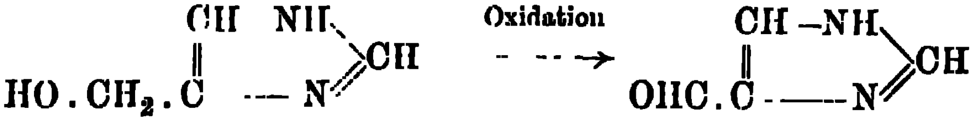
Pilosine.



Pilosinine.

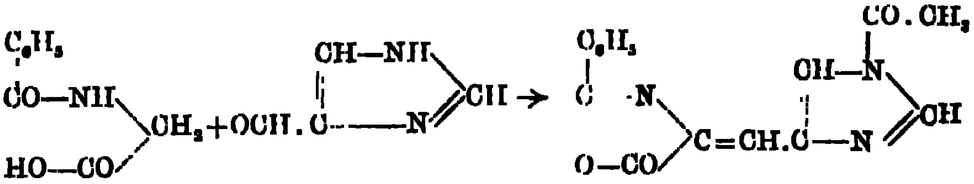
3. *The Synthesis of Histidine.*

By heating together potassium thiocyanate and the hydrochloride of diamido-acetone, amido-methyl-glyoxaline mercaptan is produced; and when this is added to dilute nitric acid, it yields 4-hydroxymethyl-glyoxaline (I.) which forms the raw material of the histidine synthesis.[7] Oxidation with chromic acid converts it into glyoxaline formaldehyde (II.)—



(I.) (II.)

By means of acetic anhydride, the formaldehyde derivative is condensed with hippuric acid to form 2-phenyl-4-[1-acetyl-glyoxaline-4-methylidine]-oxazolone (III.):—



Hippuric acid. (II.) (III.)

When this oxazolone derivative is boiled with very dilute sodium carbonate solution, the acetyl group is split off and the oxazolone ring opens. If, now, the calculated quantity of an acid be added, the compound (IV.) results. Reduction of this produces benzoyl-histidine (V.) from which histidine itself is obtained by hydrolysis—

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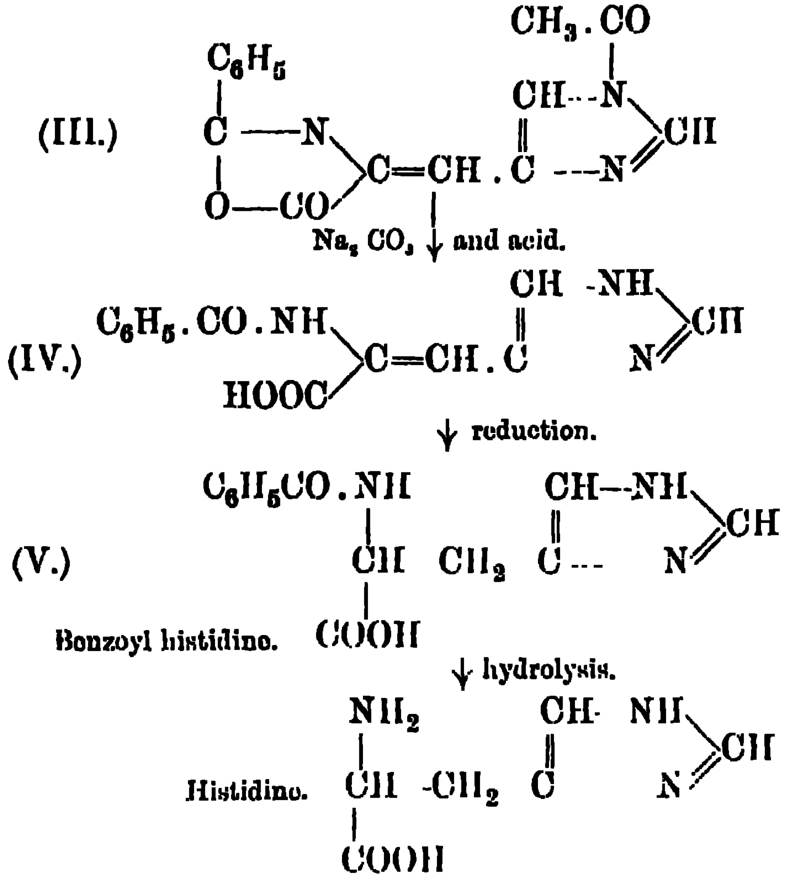
[7] Pyman, *Trans.*, 1916, **109**, 186.



I.—Some Derivatives of Ergot and their Allies.

The examination of ergot has resulted in the discovery in it of numerous compounds of physiological interest, for several of its products have marked influence upon the blood pressure system and in other directions as well. Though all the substances with which we are about to deal are not strictly alkaloids within the definition which was given at the beginning of this chapter, it seems desirable to strain a point and include them in this survey rather than omit to mention them on grounds of mere punctiliousness.

Tanret[1] discovered an active principle in ergot; but it was not until further work had been done by Barger and Carr[2] that the composition of the materials was made clear. The last two authors isolated two substances, ergotoxine, $C_{35}H_{41}O_6N_5$, and ergotinine, $C_{35}H_{39}O_5N_5$. It will be noticed that ergotoxine contains a molecule of water more than ergotinine; and subsequent investigation[1] proved that ergotinine is the lactone of ergotoxine, which is therefore a carboxylic acid. Both ergotoxine and ergotinine give on destructive distillation isobutyryl-formamide, $(CH_3)_2CH . CO . CO . NH_2$. Beyond this, nothing definite is known as to their constitution.

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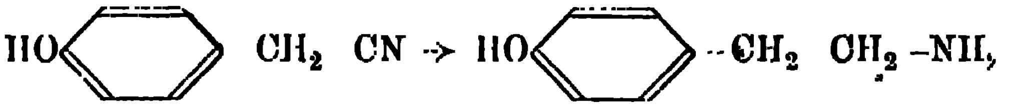
[1] Tanret, *Compt. rend.*, 1875, **81**, 896; 1878, **86**, 888; *Ann. Chim. Phys.*, 1879 (v.), **17**, 493.

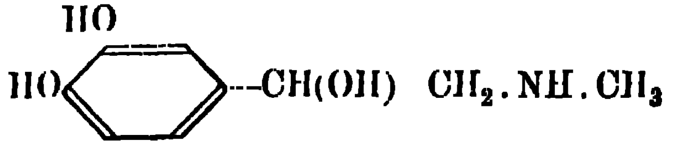
[2] Barger and Carr, *Trans.*, 1907, **91**, 336,

Further examination of ergot[2] brought to light another physiologically active substance, *p*-hydroxy-phenyl-ethylamine. This compound is also found in putrid meat.[3] It has been synthesized by the reduction, with sodium and alcohol, of *p*-hydroxy-phenyl-acetonitrile:—

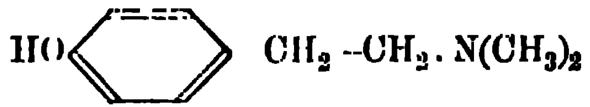


It has also been obtained in even better yield by acting on anisaldehyde, $CH_3O . C_6H_4 . CHO$, with nitromethane to form $CH_3O . C_6H_4 . CH : CH . NO_2$, which is then reduced to the amine. Demethylation of the methoxy-group completes the process.[4]

The structure of this substance is interesting, since its skeleton occurs in adrenaline,[5] the active principle of the adrenal gland and also in hordenine,[6] which is present in barley—



Adrenaline.



Hordenine.

Yet another active substance[7] was found in ergot: 4-β-amino-ethyl-glyoxaline, which is obviously closely related to histidine—

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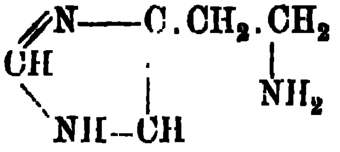
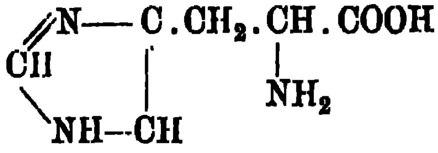
[1] Barger and Ewins, *Trans.*, 1910, **97**, 284.
[2] Barger, *Trans.*, 1909, **95**, 1123.
[3] Barger and Walpole, *J. Physiol.*, 1909, **38**, 343.
[4] Rosenmund, *Ber.*, 1909, **42**, 4778.
[5] Jowett, *Trans.*, 1904, **85**, 192.
[6] Léger, *Compt. rend.*, 1906, **142**, 108; **143**, 234, 916.
[7] Barger and Dale, *Trans.*, 1910, **97**, 2592.

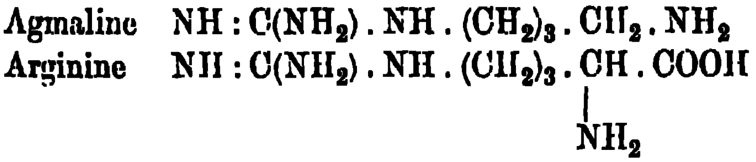


4-β-amino-ethyl-glyoxaline.



Histidine.

Finally, a substance agmaline[1] has been extracted from ergot; and it is found that it is related to the naturally occurring amino-acid arginine in exactly the same way as the glyoxaline derivative mentioned above is related to histidine—

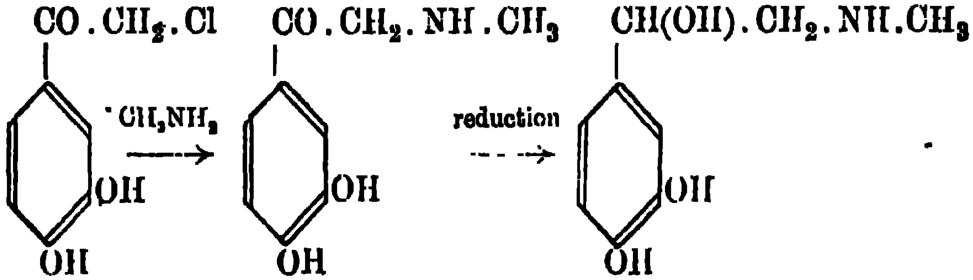


Agmaline $NH:C(NH_2).NH.(CH_2)_3.CH_2.NH_2$

Arginine $NH:C(NH_2).NH.(CH_2)_3.\underset{NH_2}{\underset{|}{CH}}.COOH$

It may be well to give the syntheses of adrenaline and hordenine, since both these substances are of interest not only on account of their physiological properties but also owing to their structural relationship to the ergot derivatives.

Adrenaline has been synthesized in the following way.[2] Catechol is treated with chloracetyl chloride to produce chloracetyl catechol (I.). The action of methylamine converts this into the ketone adrenalone (II.), which can be reduced electrolytically, or by the use of aluminium amalgam, to adrenaline (III.)—



Chloracetyl catechol. (I.)

Adrenalone. (II.)

Adrenaline. (III.)

Another method takes as its starting-point protocatechuic aldehyde. This is subjected to the cyanhydrin reaction and the cyanhydrin so formed is reduced to an amine. Methylation of the amino-group yields adrenaline. The compound formed in each case is the racemic base, from which the antipodes can be obtained by resolution of the tartrates.

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[1] Engeland and Kutscher, *Zentr. Physiol.*, 1910, **24**, 479.

[2] Stolz, *Ber.*, 1904, **37**, 4149; Dakin, *Proc. Roy. Soc.*, 1905, **76** (B), 491.

Since hordenine is the dimethyl derivative of *p*-hydroxyphenyl-ethylamine, it might be supposed that the latter would be used as a starting-point in the hordenine synthesis. Owing, however, to the readiness with which hordenine, when formed, passes into the tetra-alkyl ammonium salt form, it is found better to set out from phenyl-ethyl alcohol. This substance is converted into the corresponding chloride which, when treated with dimethyl-aniline, yields the base $C_6H_5 . CH_2 . CH_2 . N(CH_3)_2$. The missing hydroxyl radicle in the para-position is introduced by nitration, reduction, and diazotization in the usual manner. Another method consists in the methylation of *p*-methoxyphenyl-ethylamine followed by the action of hydriodic acid which splits off the methyl radicle of the methoxy-group.

With regard to the effect of structure upon physiological properties, it is interesting to note that the conversion of the alcohol adrenaline into the ketone adrenalone does not destroy the physiological activity; nor is the presence of the methyl radicle attached to the nitrogen atom essential. One hydroxyl radicle in the benzene nucleus appears to be sufficient. A marked influence is exerted by the introduction of a methyl radicle in the α- or β-position; for compounds containing this grouping are much less active than the parent substances.

CHAPTER VII

THE POLYPEPTIDES[1]

1. *Introductory.*

WHEN we examine the contents of the cells from which living tissues are built up, we find that they are for the most part composed of albuminous bodies of extremely complicated chemical character. These albumins are distinguished from all the other naturally occurring substances by the fact that animal life may be supported upon them alone in conjunction with water and salt; whereas fats and carbohydrates do not in themselves furnish nourishment sufficient for the support of animal functions for an indefinite period. The importance of the albumins from the physiological point of view, therefore, can hardly be over-estimated; while from the chemical side they furnish one of the most difficult and complicated problems which the organic chemist has yet attacked.

The difficulties of the researches which have been carried out in this branch of organic chemistry can hardly be over-estimated. In the first place, many albumins are non-crystalline substances which require special treatment before they can be obtained in crystalline form; this, of course, makes it very difficult to determine the state of purity of any specimen under consideration. Secondly, the extreme sensitiveness of albumins to heat, acids, or alcohol renders them very liable to be altered during the progress of the ordinary chemical reactions. Again, the molecular complication of these substances must be tremendous, if we are to judge from molecular weight determinations: egg albumin has been estimated to have a molecular weight of at least 15,000, according to the results of the freezing-point method.*

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[1] A complete set of references up to 1906 will be found in a lecture by Fischer (*Ber.*, 1906, **39**, 530). See also Fischer, *Ber.*, 1906, **39**, 2893; 1907, **40**, 1758, 3704; 1908, **41**, 850, 2860; Fischer and Königs, *Ber.*, 1907, **40**, 2048; Fischer and Schulze, *ibid.*, 943; Fischer and Gerngross, *Ber.*, 1909, **42**, 1485; Fischer and Luniak, *ibid.*, 4752. Fischer's papers have been reprinted in his book *Die Aminosäuren, Polypeptide und Proteine* (1906).

In the foregoing chapters we have dealt at some length with the constitutions of various compounds, and it will be remembered that there are two general methods of investigating the constitution of any given substance. We may attack the question from the synthetical side or from the analytical point of view: in the first case we study the general properties of the substance, then ask ourselves in what way we can build up a molecule whose reactions will resemble those of the one we are examining, and having synthesized this body we compare its reactions with those of the original; in the analytical method, we take the molecule to pieces in various ways, and isolate a series of decomposition products, from which we endeavour to guess the manner in which they were arranged in the original molecule. Now, in the case of the albumins, the first line of research turned upon the analytical results. This was to be foreseen, for it seemed almost impossible to build up molecules of such extreme complexity.

The oxidation of the albumins cannot be said to have yielded results of any great interest; the major part of our knowledge of these bodies has been obtained by means of hydrolysis reactions. When ferments are allowed to act upon protein derivatives, the bodies first formed are albumoses and peptones. The intermediate compounds can be further broken down into amino-acids. Hydrolysis by means of alkali takes place more rapidly; while acids decompose the albumins most easily. It is thus made clear that the substances lying at the base of the albumins belong to the class of amino-acids; and, further, that these acid nuclei are linked together in some way which allows them to be separated one from another by means of hydrolysis. It is evident that amide-formation is the most probable method of uniting the nuclei; and from this point of view Fischer took up the work of synthesizing some compounds which, while not themselves of the protein class, would show sufficient resemblance to the naturally occurring substances to allow us to deduce the probable constitution of at least part of the albumin molecule.

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* Owing to the colloidal nature of the albumins, it is unsafe to place too much reliance on the exactitude of these results.

To describe these synthetic substances, Fischer proposed the name "*Polypeptides*," by which he intends to denote those compounds which are derived from two amino-acid molecules by the elimination of water. A few polypeptides have been obtained by the hydrolysis of proteins, but by far the greater number are synthetic. We may now give the outlines of the methods employed by Fischer in his researches.

2. *Methods of Synthesizing Polypeptides.*

As a first step in polypeptide syntheses, it was necessary to obtain mono-amino-acids. This Fischer did by means of the ordinary methods—action of ammonia on the esters of bromo-fatty acids or by Strecker's cyanhydrin method (addition of hydrocyanic acid and ammonia to an aldehyde and hydrolysis of the cyanhydrin thus formed). Now, having obtained these acids, another problem presents itself. If we combine together two racemic acids we shall have not a single reaction product, but a mixture of two new racemic substances. For instance, if we start with racemic alanine and racemic leucine, we should produce a mixture of the four isomers—

d-Alanine-*d*-leucine.	*d*-Alanine-*l*-leucine.
l-Alanine-*l*-leucine.	*l*-Alanine-*d*-leucine.

The two substances in the left-hand column then combine to form a racemic substance, and the two in the right-hand column to form *another* racemic compound, so that we should have two new bodies instead of a pure compound. And, of course, if w coupled together more than two racemic acids we should find the number of stereo-isomers in the product increased in like manner. This evidently threw considerable difficulty in the way, and to avoid it Fischer resolved to use in his condensations optically active acids only. By this means he excluded the possibility of racemic compounds being formed, so that from one pair of amino-acids he obtained only a single reaction product.

This did not clear the experimental difficulties away, however; it only carried them one step further back. For, owing to the very weak acidity of the amino-acids, resolution of these substances into their optically active antipodes by salt-formation with active bases was by no means an easy task. Fischer evaded this difficulty in turn by one of his usual simple artifices. He benzoylated the amino-group of the acid, and thus reduced its basic properties to a minimum; thereafter, resolution into the optical antipodes presented no difficulty, and after this had been accomplished, the benzoyl radicle was split off and the optically active amino-acid remained.

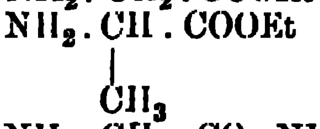
I. The first method employed by Fischer in the actual synthesis of polypeptides depends upon the elimination of a molecule of alcohol from two molecules of amino-ester—

$$NH_2 . CH_2 . COOEt + NH_2 . CH_2 . COOEt$$
$$= NH_2 . CH_2 . CO . NH . CH_2 . COOEt + EtOH$$

Now, it will be seen at once that if we applied this method as given above to a mixture of two different amino-acids, it would be sheer chance that would govern the production of the end-product. For example, if we were to combine together the two esters (A) and (B) we should get a mixture of (C) and (D) in the reaction product—

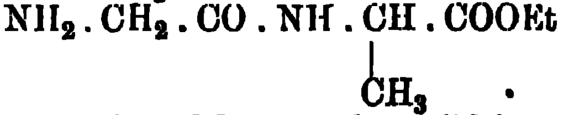
(A) $NH_2 . CH_2 . COOEt$

(B)



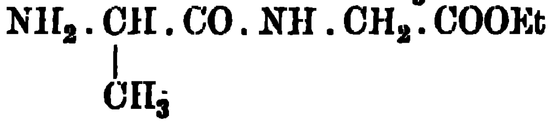
$NH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . COOEt$

(C)



$NH_2 . CH_2 . CO . NH . \underset{\displaystyle CH_3}{\underset{|}{CH}} . COOEt$

(D)



$NH_2 . \underset{\displaystyle CH_3}{\underset{|}{CH}} . CO . NH . CH_2 . COOEt$

This difficulty in its turn was overcome by Fischer in a very simple manner. Before condensing the two substances together he allowed one of them to react with ethyl chlorocarbonate, which acted upon the amino-group and protected it from further attack—

$$Cl . COOEt + NH_2 . CH_2 . COOEt$$
$$= EtOOC . NH . CH_2 . COOEt + HCl$$

When a compound such as this is heated for thirty-six hours with the ester of an amino-acid, alcohol is eliminated between the $—NH_2$ group of the amino-acid and the $—CH_2 . COOOEt$

group of the above substance, whose amino-group cannot react in this way. Thus we know at once the constitution of the resulting compound. An example will serve to make the matter clear. If we start with the substance glycyl-glycine,* and treat it with chloro-carbonic ester, we shall obtain the substance shown below, glycyl-glycine carboxylic acid ester—

$$\begin{aligned}&\mathrm{EtOOC\,.\,Cl + NH_2\,.\,CH_2\,.\,CO\,.\,NH\,.\,CH_2\,.\,COOEt}\\&\quad\mathrm{= EtOOC\,.\,NH\,.\,CH_2\,.\,CO\,.\,NH\,.\,CH_2\,.\,COOEt + HCl}\end{aligned}$$

When this substance is heated for thirty-six hours with leucine ester, ethyl alcohol is eliminated in the following way:—

$$\begin{aligned}&\mathrm{EtOOC.NH.CH_2.CO.NH.CH_2.COOEt + NH_2.CH.(C_4H_9).COOEt}\\&\quad\mathrm{= EtOOC.NH.CH_2.CO.NH.CH_2.CO.NH.CH(C_4H_9).COOEt}\end{aligned}$$

This substance is the carboxylic ester of glycyl-glycine-leucine; as can be seen from the formulæ, it can have no other constitution than that shown. This carbethoxy-glycylglycyl-leucine ester contains three amino-acid nuclei, and is therefore called a tri-peptide derivative.

II. The yields of end-product from the foregoing method of synthesis were poor, and Fischer therefore turned to another way of attaining his objective. When the ester of the chlorocarbonic derivative of an amino-acid is treated with thionyl chloride, an acid chloride is formed; and this readily condenses with amino-esters, forming polypeptide derivatives. For instance, if we start again with the derivative obtained by the action of chlorocarbonic ester upon glycylglycine, and treat it with thionyl chloride, we shall produce the chloride whose constitution is shown below—

$$\mathrm{EtOOC\,.\,NH\,.\,CH_2\,.\,CO\,.\,NH\,.\,CH_2\,.\,CO\,.\,Cl}$$

When this chloride is condensed with glycylglycine ester—

$$\mathrm{NH_2\,.\,CH_2\,.\,CO\,.\,NH\,.\,CH_2\,.\,COOEt}$$

it yields the tetra-peptide derivative, glycylglycylglycylglycine-carbethoxy-ester—

$$\mathrm{EtOOC.NH.CH_2\,CO.NH.CH_2\,CO.NH.CH_2.CO.NH.CH_2\,COOEt}$$

---

* Fischer terms "glycyl" the radicle $\mathrm{NH_2\,.\,CH_2\,.\,CO}$— which is derived from glycine (glycocoll) $\mathrm{NH_2\,.\,CH_2\,.\,COOH}$.

III. The drawback of the two foregoing methods lies in the fact that, so far, no method has been discovered by means of which we can eliminate the group—COOEt, which is attached to one end of the polypeptide chain; so that neither method can be employed to build up a true polypeptide. Fischer therefore devised another method by means of which the polypeptides themselves can be produced. Starting from the ester of a substance like glycine (I.) or glycylglycine, he treated this with chloracetyl chloride (II.) or some similar compound. Hydrochloric acid is eliminated, and the two molecules combine together to form a compound with chlorine at one end of the chain (III.). The ester group at the other end of the chain is then hydrolysed very carefully, and a chloro-acid produced (IV.), which, on treatment with ammonia, yields a true polypeptide (V.)—

(I.) $NH_2 . CH_2 . COOEt$
(II.) $Cl . CH_2\ CO . Cl$
(III.) $Cl . CH_2 . CO . NH . CH_2 . COOEt$
(IV.) $Cl . CH_2 . CO . NH . CH_2 . COOH$
(V.) $NH_2 . CH_2 . CO . NH . CH_2 . COOH$

The reason for hydrolysing the ester (III.) to the acid (IV.), lies in the fact that, if this were not done, an amide would be formed on treatment with ammonia, and the amido-group would be most difficult to get rid of later.

IV. A variation of the previous method may also be used. If we take the substance—

$$Cl . CH_2 . CO . NH . CH_2 . COOH$$

which was formed in the course of the last synthesis we described, and treat it with pentachloride of phosphorus, we convert the acid into the chloride *—

$$Cl . CH_2 . CO . NH . CH_2\ CO . Cl$$

---

* Thionyl chloride is a better reagent than phosphorus pentachloride for producing acid chlorides. The reaction takes place according to the equation—

$$R . COOH + SOCl_2 = R . CO . Cl + SO_2 + HCl$$

from which it will be clear that the acid chloride can be obtained pure simply by boiling off the sulphur dioxide and hydrochloric acid.

which can then be made to interact with glycine ester, yielding the more complicated substance—

$$\mathrm{Cl . CH_2 . CO . NH . CH_2 . CO . NH . CH_2\ COOEt}$$

The remaining chlorine atom may then be replaced by the amino-group by means of ammonia; and after hydrolysis of the ester group the tri-peptide glycylglycylglycine is formed—

$$\mathrm{NH_2.CH_2.CO.NH.CH_2.CO.NH.CH_2.COOH}$$

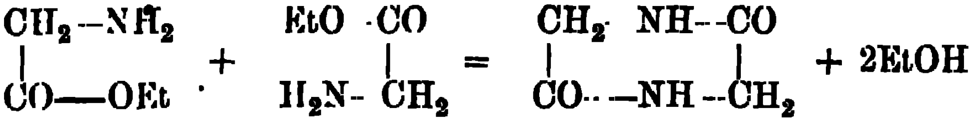
V. This modification has been further extended. When amino-acids are treated with a mixture of acetyl chloride and phosphorus pentachloride, the corresponding acid chlorides are formed. These can be combined with other amino-acids, and in this way we can obtain polypeptides. For instance, if we take glycine and treat it as described we should expect to produce glycyl chloride—

$$\mathrm{NH_2.CH_2.COOH} \rightarrow \mathrm{NH_2.CH_2.CO.Cl}$$

This can be condensed with another molecule of glycine, forming glycylglycine—

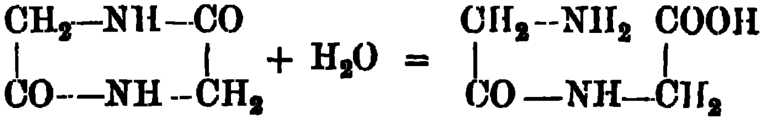
$$\mathrm{NH_2.CH_2.CO.Cl + NH_2.CH_2.COOH = NH_2.CH_2.CO.NH.CH_2.COOH}$$

VI. If we abstract two molecules of alcohol from two molecules of an *α*-amino-ester, a cyclic substance is produced, which is a derivative of *αγ*-diketo-piperazine—



$$\begin{array}{l} \mathrm{CH_2-NH_2} \\ | \\ \mathrm{CO-OEt} \end{array} + \begin{array}{r} \mathrm{EtO-CO} \\ | \\ \mathrm{H_2N-CH_2} \end{array} = \begin{array}{l} \mathrm{CH_2-NH-CO} \\ |\qquad\qquad\ | \\ \mathrm{CO-NH-CH_2} \end{array} + \mathrm{2EtOH}$$

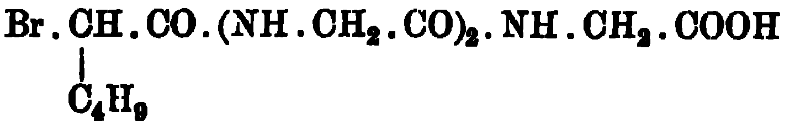
This cyclic compound, when carefully treated with hydrochloric acid, can be opened out into an open-chain body, glycylglycine—



$$\begin{array}{l} \mathrm{CH_2-NH-CO} \\ |\qquad\qquad\ | \\ \mathrm{CO-NH-CH_2} \end{array} + \mathrm{H_2O} = \begin{array}{l} \mathrm{CH_2-NH_2\ \ COOH} \\ |\qquad\qquad\quad | \\ \mathrm{CO-NH-CH_2} \end{array}$$

By choosing the appropriate amino-ester from which to start, a given polypeptide may be obtained in this manner.

We cannot go into details with regard to the various substances which have been synthesized by means of the foregoing methods, but there is one substance which is worthy of mention. Fischer eventually synthesized an octadecapeptide in the following manner. Starting from dextro-*a*-bromo-isocapronyl-diglycylglycine—

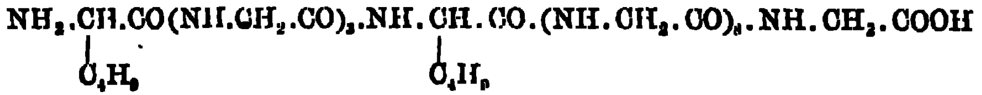


$$\underset{\displaystyle C_4H_9}{Br.\overset{}{CH}}.CO.(NH.CH_2.CO)_2.NH.CH_2.COOH$$

he treated this according to the fourth method, combining it with penta-glycylglycine, and, finally, exchanging the bromine atom for an amino-group, he obtained lævo-leucyl-octaglycylglycine—

$$NH_2.\underset{\displaystyle C_4H_9}{CH}.CO.(NH.CH_2.CO)_8.NH.CH_2.COOH$$

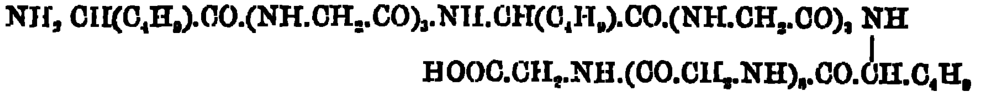
This polypeptide was then coupled with dextro-bromo-isocaproyl-diglycylglycine, and again treated with ammonia, whereby the tetradecapeptide shown below was formed—



$$NH_2.\underset{\displaystyle C_4H_9}{CH}.CO(NH.CH_2.CO)_3.NH.\underset{\displaystyle C_4H_9}{CH}.CO.(NH.CH_2.CO)_8.NH.CH_2.COOH$$

Lævo-leucyl-triglycyl-lævo-leucyl-octaglycyl-glycine.

By a repetition of this series of reactions the octadecapeptide was formed, which has the constitution shown below—



$$\begin{array}{l} NH_2\,CH(C_4H_9).CO.(NH.CH_2.CO)_3.NH.CH(C_4H_9).CO.(NH.CH_2.CO)_3\,NH \\ \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad HOOC.CH_2.NH.(CO.CH_2.NH)_8.CO.CH.C_4H_9 \end{array}$$

l-Leucyl-triglycyl-*l*-leucyl-triglycyl-*l*-leucyl-octaglycyl-glycine.

This extraordinary substance is apparently one of the most complicated systems of known constitution which has hitherto been synthesized. Its molecular weight is 1213, while that of the fairly complicated natural body, tri-stearin, is only 891.

3. *The Resemblances between the Polypeptides and the Proteins.*

We must now briefly summarize the main characteristics of the polypeptide class, and it may be of interest to compare them with those of the naturally occurring proteins. The polypeptides are solids, which usually melt at about 200° C., with some decomposition. They are easily soluble in water, but insoluble in alcohol, like some of the albumins; and instead of having the usual insipid or sweet taste of the ordinary amino-acid, they are bitter, like the protein derivatives. In dilute sulphuric acid solution they are precipitated by phosphotungstic acid, in which behaviour they resemble the albumins. Both the natural and artificial classes give the biuret reaction. The action of ferments, or of acids or alkalis, is the same in both classes; and similar products are obtained when animals are fed with polypeptides and albumins. In the case of ferment action it is found that much depends upon the groups which have been used in building up the polypeptide structure, some polypeptides being much more easily fermented than others.

4. *The Proteins.*

In order to see the results of the polypeptide investigations in their true perspective, it is necessary to glance briefly at the chemistry of the proteins. No attempt will be made to enter into the subject in detail, as it belongs to bio-chemistry rather than to pure organic chemistry; and the description of the properties of many ill-defined classes of compounds would merely prove wearisome without adding much to the information of the reader.

The proteins are nitrogenous materials which comprise the most important portion of the contents of cells in the animal body and which also occur in plants. They form the main constituents of animal nourishment and are thus converted into the substances from which the organized part of the animal frame is constructed. It is evident that they are of the greatest importance in vital processes.

The chemical investigation of this group of substances is beset with many difficulties, some of which are due to the colloidal nature of many proteins, while others arise from the complexity of the protein structure. Even the classification of the proteins is of the roughest nature, depending upon their solubility in various reagents and similar characteristics. Thus it is very difficult to decide, in some cases, whether a protein should be placed in one class or another; and this must be borne in mind lest the nomenclature should lead the reader to imagine that there is as sharp a distinction between, say, an albumin and a globulin as there is between an aliphatic acid and an aromatic alcohol.

The albumins, of which white of egg is a common example, are proteins soluble in water, from which they can be separated again by salting out. On heating, they undergo coagulation.

The globulins, on the other hand, are almost insoluble in water, but dissolve in dilute acids, alkalis, or salt solutions. They are coagulated on heating, and are precipitated from saturated solutions of magnesium sulphate, in which respect they resemble the albumins.

The sclero-proteins, such as gelatine and keratine, are distinguished by the fact that they form sticky, gelatinous materials when treated with water. They are also characterized by the readiness with which they dissolve in alcohol.

Allied to the foregoing are the protamines and histones, which are of a much simpler nature than the members of the first three classes. Of the two, the protamines are the more basic in character; while the histones stand midway between them and the albumins in this respect. Both classes are found in fish sperm, generally combined with nucleic acid.

The next group of compounds is more complex in certain ways; for in addition to the ordinary type of albumin structure they contain other groups of a different nature, and they are therefore to be regarded as conjugated proteins.

The conjugated proteins may be divided into three classes according to the "prosthetic group" which they contain. In the case of those substances which contain nucleic acids, the class is termed nucleo-proteins; when a carbohydrate group is present, the compound belongs to the gluco-proteins; whilst if the prosthetic group be chromatogen, the body belongs to the chromo-protein series. Logically, the phospho-proteins and the lecitho-proteins ought also to be included under the heading of conjugated proteins.

Turning now to derivatives of the proteins and treating them in a descending order of complexity, the first class includes the meta-proteins. These are obtained by treating complex proteins with acid, which gives rise to acid-albumins, or with alkali, which yields alkali-albumins. The acid-albumins are insoluble in water or salt solutions, but soluble in dilute hydrochloric acid or sodium carbonate solution. The alkali-albumins are insoluble in water or salt solutions. The main difference between the two classes is that the acid-albumins have no effect upon calcium carbonate, whereas the alkali-albumins liberate carbon dioxide from it.

The next class of protein derivatives contains the proteoses such as albumose, globulose, etc. These substances can be obtained from the albumins by hydrolytic decomposition in presence of certain enzymes. They are soluble in water even when their parent substances were insoluble; and the further the decomposition has proceeded, the more readily soluble the product appears to be. They can be salted out of solution by means of ammonium sulphate in presence of acetic acid.

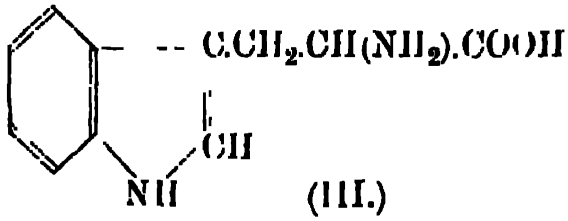
Closely allied to the proteoses are the peptones, the main difference between the two classes being that the peptones are not thrown out of solution in presence of ammonium sulphate.

Finally, when the fission of the protein molecule has been carried to its furthest stages, the polypeptides and the simple amino-acids are reached.

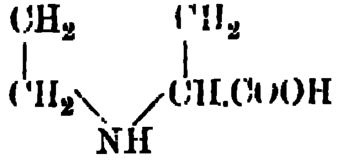
It must not be supposed that the foregoing simplified scheme includes all the degradation products of protein molecules. In addition to amino-acids, certain hydroxy-amino-acids and simple fatty acids have been isolated; while sulphur derivatives such as cysteine (I.) and its oxidation product cystine (II.) are found. Tryptophane (III.) and proline (IV.) have also been recognized in some cases.

$HS.CH_2.CH(NH_2).COOH$ (I.)

$[S.CH_2.CH(NH_2).COOH]_2$ (II.)



(III.)



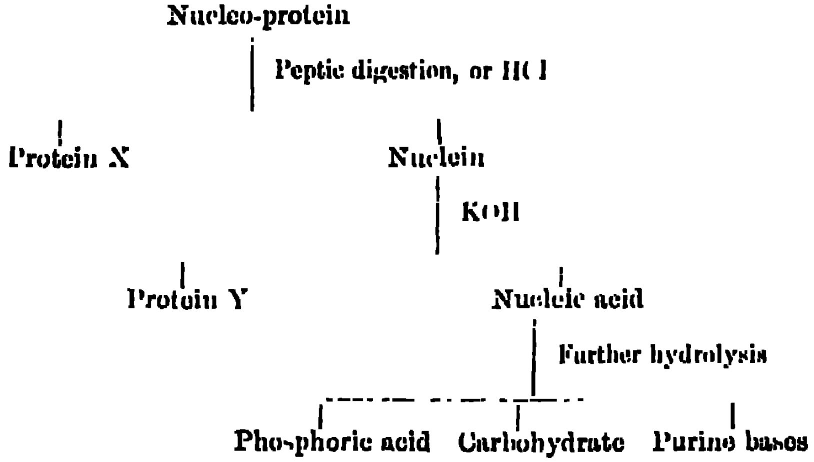
(IV.)

Carbohydrate derivatives have been detected, including a nitrogenous compound glucosamine—

$$CH_2OH.CH(OH).CH(OH).CH(OH).CH(NH_2).CHO$$

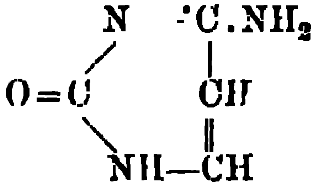
and the action of putrefying bacteria results in the formation of the diamines: putrescine $NH_2.(CH_2)_4.NH_2$ and cadaverine, $NH_2.(CH_2)_5.NH_2$.

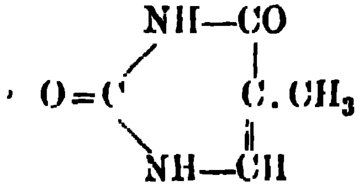
When a nucleo-protein is subjected to reagents which break it down the process is a complex one:



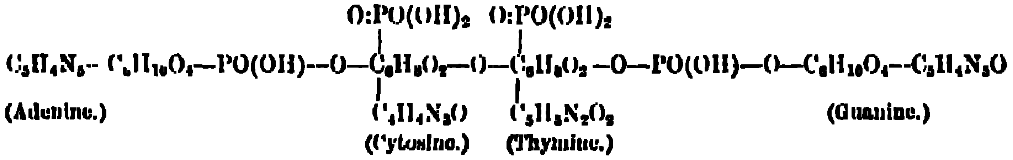
From this scheme it can be seen that when a nucleo-protein is acted on by pepsin or is hydrolysed by means of dilute hydrochloric acid, it breaks down into two portions, one of which is a protein and the other a nuclein. Further hydrolysis decomposes the nuclein with the liberation of a second portion of protein, which may be different in constitution from the protein obtained in the previous hydrolysis; while a nucleic acid forms the remainder of the fission-products. Further decomposition of the nucleic acid yields various molecules belonging to the carbohydrate and purine groups and also phosphoric acid.

The constitution of the nucleic acids is not yet definitely established; but in the case of nucleic acid derived from the thymus gland the following decomposition products have been isolated: phosphoric acid, a hexose, two purine derivatives (guanine and adenine), and two pyrimidine derivatives, (cytosine and thymine). Guanine is 2-amino-6-oxy-purine and adenine is 6-amino-purine. Cytosine and thymine have the structures shown below:


Cytosine.


Thymine.

It has been tentatively suggested that thymus nucleic acid has the following structure[1]; but it must be regarded as merely a probable conjecture and not as an established view.



$$\underset{\text{(Adenine.)}}{C_5H_4N_5}—C_6H_{10}O_4—PO(OH)—O—\underset{\underset{\text{(Cytosine.)}}{C_4H_4N_3O}}{\overset{O:PO(OH)_2}{C_6H_8O_2}}—O—\underset{\underset{\text{(Thymine.)}}{C_5H_5N_2O_2}}{\overset{O:PO(OH)_2}{C_6H_8O_2}}—O—PO(OH)—O—C_6H_{10}O_4—\underset{\text{(Guanine.)}}{C_5H_4N_5O}$$

The foregoing sketch is sufficient to show the extreme complexity of the protein structure; and it indicates in no uncertain way how far we still have to travel before we are able to make a definite statement with regard to the constitution of even the simplest member of the protein class. At the present time, the upper limit of laboratory syntheses is reached with comparatively simple polypeptides; but above that lie the peptones, proteoses and meta-proteins, all increasing in complexity; and then come the proteins proper. Nor is this all; for we have still to clear up the constitutions of the conjugated proteins with their nucleic acid, carbohydrate or chromatogen groups.

It will be seen that the problem of the cellulose constitution, which has hitherto defied the efforts of organic chemists, is a mere elementary exercise when compared with the complexity of the protein molecule; for in the case of celluloses we have to deal with only the three elements carbon, hydrogen, oxygen; and the decomposition products involved in the reactions of the compound are almost entirely confined to the sugar group: whereas in the proteins the introduction of the extra elements nitrogen and sulphur complicates the riddle, owing to the possible existence of many further types of linkage between the atoms.

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[1] Levene and Jacobs, *J. Biol. Chem.*, 1912, **12**, 377.

CHAPTER VIII

THE CHLOROPHYLL PROBLEM

1. *Introductory*

THE chemical constitution of the green colouring matter of plants offers a problem which has taxed the ingenuity of many investigators. Even so recently as five years ago our knowledge of the chlorophyll structure was so fragmentary and disconnected that the very name of the substance was omitted from standard textbooks. But since then the compound has been submitted to rigorous scrutiny, its reactions have been classified, its decomposition products brought into relation to each other; and although our views on the exact nature of its structure are still fluid, the information at our disposal is sufficient to render a coherent account of it possible.[1]

In the present chapter an attempt will be made to link together the scattered data of the subject in a more or less connected scheme,[*] and to present to the reader a summary of the important information which has been acquired. In this branch of chemistry, theory has in many cases far outrun practice; and constitutional formulæ have been proposed for some substances the true structures of which are possibly different from those assumed for them. Under these circumstances an endeavour will be made here to indicate as clearly as possible the points at which established facts end and pure hypotheses begin; for it seems desirable to draw the line of demarcation as sharply as can be done. Some of the formulæ ascribed to certain compounds may be accurate, though yet unproved; but it would be doing the reader a poor service to leave him in doubt as to their actual present value, or to try to persuade him into an acceptance of constitutions which later work may prove to be erroneous.

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[1] For a general account of recent researches by Willstätter, see *Ber.*, 1914, 47, 2831.

[*] The reader is advised to make use of the table at the end of this volume in any difficulty which may arise as to the relations between certain chlorophyll derivatives.

A study of the literature on chlorophyll is beset with difficulties. In the first place, the nomenclature of the subject is to a large extent new and different from that with which the organic chemist is familiar; for instead of referring to acids in the usual terms, the investigators have christened them with a brand-new set of names, and as these titles have established themselves in the literature, it is hopeless to expect that they will be altered now. Secondly, chlorophyll contains within its molecule a complex and sensitive grouping capable of undergoing various intramolecular changes under the action of reagents; and these rearrangements form one of the most puzzling factors in the problem.

The extraction of chlorophyll from plants is a simple operation. The leaves are removed from their stems, dried and powdered. Alcohol is then poured over the powder and the mixture kept constantly stirred. After a longer or shorter time the chlorophyll passes into the liquid, from which it can be extracted. By this process a "crystalline chlorophyll" is obtained; whereas when ether is substituted for alcohol, an "amorphous chlorophyll" is found in solution.[1]

The composition of "amorphous chlorophyll" may be regarded provisionally as corresponding to $C_{55}H_{72}N_4O_5Mg$; but even here a word of caution is desirable. The lowest possible molecular weight of a substance such as this would reach nearly 900; and reflection will show that the exact analysis of so complex a compound must be difficult in the extreme.

The complication of the formula makes it obvious that our chief knowledge of chlorophyll must be gained through an acquaintance with its degradation products. Three main types of reaction might be employed to break down the chlorophyll molecule: oxidation, reduction, and hydrolysis. In practice, it has been found that most information is gained from a study of the last class; for oxidation and reduction proved to be comparatively useless in so far as the production of immediate decomposition products is concerned.

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[1] Willstätter and Benz, *Annalen*, 1908, **358**, 267; Willstätter and Oppé. *ibid.*, 1911, **378**, 1.

Along with chlorophyll, two other colouring matters are found in leaves. The one, carotin, is coppery in colour and is identical with the substance which gives their colour to carrots. It is a hydrocarbon of the composition $C_{40}H_{56}$. The other colouring material, xanthophyll, is dark brown-red in tint; has the composition $C_{40}H_{56}O_2$; and seems to be an oxidation product of carotin.[1] It is suggested that in summer the green of chlorophyll masks the tints of carotin and xanthophyll; but when in autumn the chlorophyll decays, the reddish pigments become visible and give the leaves their autumn colouring.

It is interesting to note that the chlorophyll of brown algæ is identical with that derived from land-plants,[2] a fact which appears most unexpected from the tints of the organisms.

2. *Amorphous Chlorophyll and so-called "Crystalline Chlorophyll."*

As has been pointed out already, the extraction of chlorophyll from plants by means of ether yields an amorphous substance. Specimens of this amorphous product were obtained, under carefully regulated conditions, from about two hundred different kinds of plants; and, on examination, it was found that all the samples yielded on decomposition approximately the same amount—about 30 per cent. of an alcohol named phytol.[3] This at once suggests that amorphous chlorophyll may be the phytyl ester of some unknown acid.

Confirmation of this view was obtained by hydrolysing amorphous chlorophyll with cold dilute potash. The products of the reaction are equimolecular quantities of methyl alcohol, phytyl alcohol, and the potassium salt of a tribasic acid, which is termed chlorophyllin.[4] It appears, then, that amorphous chlorophyll is a di-ester of this tribasic acid, chlorophyllin, in which one of the carboxyl groups is esterified with methyl alcohol, another with phytyl alcohol, whilst the third is occupied in some other manner.

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[1] Willstätter and Mieg, *Annalen*, 1907, **355**, 1.

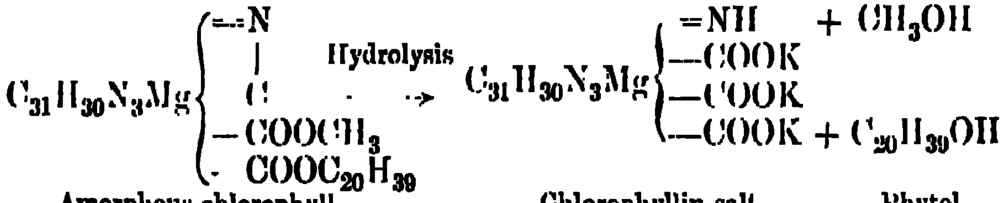
[2] Willstätter and Page, *Annalen*, 1914, **404**, 237.

[3] Willstätter, Hocheder, and Hug, *Annalen*, 1909, **371**, 1; Willstätter and Oppé, *ibid.*, 1911, **378**, 1.

[4] Willstätter and Stoll, *Annalen*, 1910, **378**, 18.

But three carboxyl radicles would imply the presence of six oxygen atoms in the chlorophyll molecule; whereas from the analytical results there appear to be only five. The possibility of internal anhydride formation is excluded by the fact that phytochlorin-*e* (a decomposition product of chlorophyll) contains the same grouping and does not form an amide with ammonia.[1] Since nitrogen atoms are found in the molecule, it might be assumed that the third acidic group is present as an amide; but in this case, ammonia would be found in the products of hydrolysis. The only feasible explanation is that the fifth oxygen atom of amorphous chlorophyll forms part of a lactam ring which is opened up on hydrolysis, setting free the third carboxyl group.*

Now since phytyl alcohol has the formula $C_{20}H_{39}OH$, it follows that on the above assumption we can express the hydrolysis reaction thus—



$$C_{31}H_{30}N_3Mg\begin{cases} =N \\ \quad | \\ \quad C \\ -COOCH_3 \\ -COOC_{20}H_{39} \end{cases} \xrightarrow{\text{Hydrolysis}} C_{31}H_{30}N_3Mg\begin{cases} =NH \quad + CH_3OH \\ -COOK \\ -COOK \\ -COOK + C_{20}H_{39}OH \end{cases}$$

Amorphous chlorophyll. Chlorophyllin salt. Phytol.

The case of "crystalline chlorophyll" must now be examined. It also is found to be a di-ester: but instead of the phytyl radicle it contains an ethyl group; the second carboxyl radicle is esterified with methyl alcohol; whilst the third carboxyl resembles the corresponding one of amorphous chlorophyll. Thus, during the extraction of chlorophyll with alcohol, it is clear that the phytyl group has been replaced by an ethyl radicle. This process is traced to the action of an enzyme, chlorophyllase, which is found in plants. During prolonged processes of maceration with alcohol, the chlorophyllase from the plant tissues substitutes ethyl for phytyl alcohol, and "crystalline chlorophyll" is the result.[1]

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[1] Willstätter and Utzinger, *Annalen*, 1911, **382**, 129.

* It will be noted that at this point difficulties arise as to the exact hydrogen content of these bodies. When the lactam chlorophyll is converted into the acid chlorophyllin an atom of hydrogen is taken up by the imido group. Willstätter's formulæ take no account of this (*e.g.*, *Annalen*, 1911, **378**, 25). To avoid confusion, the present account takes as a starting-point the composition of chlorophyll-*a* as given by Willstätter in *Annalen*, 1912, **390**, 227; and it must be read accordingly.

As "amorphous chlorophyll" is a crude term, it may now be replaced by something more scientific, if equally cumbrous. When one carboxyl radicle of the tribasic acid termed chlorophyllin is esterified with methyl alcohol, the product is called chlorophyllide. If now a second carboxyl group in chlorophyllide be esterified with phytyl alcohol, the new substance is termed phytyl chlorophyllide. "Crystalline chlorophyll" is obviously ethyl chlorophyllide. The following formulæ* show the relations between the four compounds:—

$$C_{31}H_{30}N_3Mg\left\{\begin{array}{l}=NH\\ -COOH\\ -COOH\\ -COOH\end{array}\right.$$

Chlorophyllin.

$$C_{31}H_{30}N_3Mg\left\{\begin{array}{l}NH\\ -COOH\\ -COOCH_3\\ -COOH\end{array}\right.$$

Chlorophyllide.

$$C_{31}H_{30}N_3Mg\left\{\begin{array}{l}NH\\ COOH\\ -COOCH_3\\ -COOC_{20}H_{39}\end{array}\right.$$

Phytyl chlorophyllide
(Amorphous chlorophyll).

$$C_{31}H_{30}N_3Mg\left\{\begin{array}{l}NH\\ COOH\\ -COOCH_3\\ COOC_2H_5\end{array}\right.$$

Ethyl chlorophyllide
(Crystalline chlorophyll).

These formulæ are given with all radicles free for the sake of clearness, but actually the amino-group and the neighbouring carboxyl probably form the lactam ring immediately. The evidence on this point is given in § 7.

3. *The Structure of Phytol.*

Owing to the great difficulty involved in purifying the decomposition products of phytol, the investigation of its constitution has proved extremely hard; and some erroneous data were given in the first paper on the subject[2] which have now been corrected.[3]

Phytol has the composition $C_{20}H_{39}.OH$. It is therefore a member of the ethylene or the polymethylene series. The results of oxidation prove it to be an ethylenic compound. It occurs in two isomeric forms which differ from each other in the ease with which water is eliminated from the molecule. This points to its showing geometrical isomerism.

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[1] Willstätter and Stoll, *Annalen*, 1910, **378**, 18.

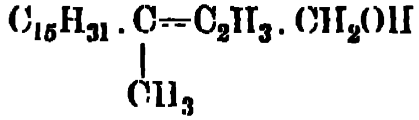
* See footnote on p. 200.

[2] Willstätter, Meyer, and Hüni, *Annalen*, 1910, **378**, 73.

[3] Willstätter, Schuppli, and Mayer, *Annalen*, 1919, **418**, 121.

When oxidized, it is converted into an acid, phytenic acid, $C_{19}H_{37}.COOH$; and as this contains the same number of carbon atoms as phytol itself, the original phytol must be a primary alcohol, $C_{19}H_{37}.CH_2OH$.

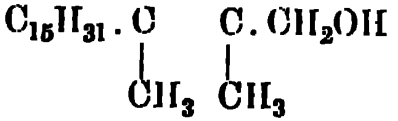
Oxidation with chromic acid produces a ketone, $C_{17}H_{34}O$, the reaction having evidently broken the phytol chain at the double bond. Since three carbon atoms are split off during this oxidation, we are justified in writing the phytol structure thus:



$$\underset{\displaystyle CH_3}{C_{15}H_{31}.\overset{}{C}}{=}C_2H_3.CH_2OH$$

The methyl group attached to the ethylenic carbon atom is necessary in order to produce a ketone and not an acid upon oxidation.

Now the group $:C_2H_3—$ must have either of the structures $:C(CH_3)\text{- -}$ or $:CH.CH_2.CH_2.OH$; so that the formula for phytol must be:

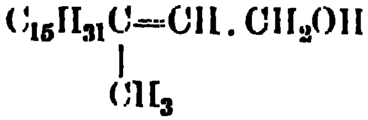


$$C_{15}H_{31}.\underset{CH_3}{C}\quad\underset{CH_3}{C}.CH_2OH$$

Phytol.

(I.)

or



$$C_{15}H_{31}\underset{CH_3}{C}{=}CH.CH_2OH$$

(II.)

The alternative structure (II.) appears to be excluded, owing to the fact that phytenic acid forms a lactone, which is a reaction characteristic of acids containing methyl groups in the α- and β-positions and a double bond in the Δ^1-position, as is the case in the phytol formula given above.

4. *Chlorophyll-a and Chlorophyll-b.*

Half a century ago Stokes[1] proved that the chlorophyll occurring in plants is a mixture of two substances differing in their spectra and solubilities in certain solvents; but his paper remained almost unnoticed by later workers, and it was not until 1912 that definite chemical corroboration of his statements was obtained.[1]

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[1] Stokes, *Proc. Roy. Soc.*, 1864, **13**, 144; compare Tswett, *Zeit. Biol.*, 1907, **5**, 6; *Ber. deutsch. bot. Ges.*, 1906, **24**, 316; 1907, **25**, 137; *Ber.*, 1908, **41**, 1352.

The newer researches on the subject started from a different standpoint. When chlorophyll was treated with certain reagents, it was found that it yielded a mixture of two substances: phytochlorin-*e* and phytorhodin-*g*. These compounds are found to occur among the degradation products of chlorophyll in the almost constant proportion of five molecules of phytochlorin-*e* to two molecules of phytorhodin-*g*. At first sight it appears easy to account for this by assuming that the chlorophyll skeleton contains five phytochlorin nuclei and two phytorhodin nuclei; so that in its decomposition it could give rise to the products in the required proportions. This explanation breaks down at once, however, when it is shown that the molecular weights of phytochlorin and phytorhodin are each approximately the same as that of chlorophyll itself, if we deduct from the latter the molecular weight of the phytyl radicle which does not occur in either the phytochlorin or the phytorhodin molecule. Clearly, if the molecular weight of phytochlorin-*e* is nearly the same as that of the non-phytyl part of the chlorophyll molecule, there is no room in the latter substance for five phytochlorin nuclei.

Evidently only one way can be found out of the difficulty. It is necessary to assume that chlorophyll is a mixture of two components, one of which on degradation produces phytochlorin-*e* whilst the other gives rise to phytorhodin-*g*. This view has actually been proved correct[2] by the separation of chlorophyll into two portions: chlorophyll-*a* and chlorophyll-*b*. By shaking a solution of chlorophyll in petroleum ether with some water containing methyl alcohol it is found that chlorophyll-*a* remains in the petroleum ether whilst the chlorophyll-*b* passes into the aqueous layer.

Chlorophyll-*a* is a bluish-black in tint; contains half a molecule of water of crystallization; and gives only phytochlorin-*e* when it is decomposed. Chlorophyll-*b* is greenish-black in colour; its crystals are anhydrous; and when it is broken down it yields only phytorhodin-*g*. On analysis, chlorophyll-*a* is found to be—

---

[1] Willstätter and Isler, *Annalen*, 1912, 390, 269.

[2] *Ibid.*

$$[C_{32}H_{30}ON_4Mg](COOCH_3)(COOC_{20}H_{39}) + \tfrac{1}{2}H_2O$$

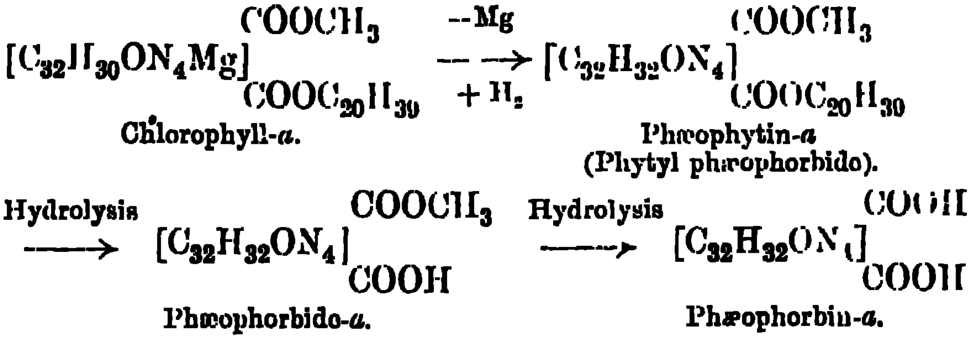
whilst chlorophyll-*b* gives results corresponding to—

$$[C_{32}H_{28}O_2N_4Mg](COOCH_3)(COOC_{20}H_{39})$$

5. *Phæophytins and Phæophorbides.*

When chlorophyll-*a* or chlorophyll-*b* is treated with alcoholic oxalic acid, the magnesium atom of the molecule is removed and replaced by two hydrogen atoms.* In this reaction the ester groups of the molecule are left intact. The product of the reaction is clearly the methyl-phytyl ester of the hydrogen derivative of chlorophyll. It is termed a phæophytin; and the suffix "*a*" or "*b*" is used to indicate from which of the chlorophylls it is derived.[1]

Further treatment hydrolyses away the phytyl radicle, leaving a monomethyl ester, which is called a phæophorbide. Finally, removal of the methyl radicle leaves a dibasic acid, phæophorbin. The following scheme will make the matter clear:—



$$[C_{32}H_{30}ON_4Mg]\begin{matrix}COOCH_3\\COOC_{20}H_{39}\end{matrix} \xrightarrow[+H_2]{-Mg} [C_{32}H_{32}ON_4]\begin{matrix}COOCH_3\\COOC_{20}H_{30}\end{matrix}$$

Chlorophyll-*a*. Phæophytin-*a* (Phytyl phæophorbide).

$$\xrightarrow{\text{Hydrolysis}} [C_{32}H_{32}ON_4]\begin{matrix}COOCH_3\\COOH\end{matrix} \xrightarrow{\text{Hydrolysis}} [C_{32}H_{32}ON_4]\begin{matrix}COOH\\COOH\end{matrix}$$

Phæophorbide-*a*. Phæophorbin-*a*.

As has already been remarked, the nomenclature of the chlorophyll derivatives differs from that usually employed in organic chemistry; and therefore it may render the task of the reader easier if some indication be given at this point of the relations between the various groups of compounds with which it is necessary to deal in this chapter. The two main classes are the magnesium-containing derivatives and the magnesium-free substances which are derived from the others by replacing the magnesium by two hydrogen atoms:—

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* The reverse change (replacement of hydrogen by magnesium) can be carried out by heating the substance with magnesium oxide and caustic potash solution or by the action of the Grignard reagent (Willstätter and Forsén, *Annalen*, 1913, **396**, 180).

[1] Willstätter and Isler, *Annalen*, 1912, **390**, 269.

MAGNESIUM DERIVATIVES.	CORRESPONDING COMPOUNDS WHEREIN THE MAGNESIUM ATOM IS REPLACED BY TWO HYDROGEN ATOMS.
* *Chlorophyllin* $MgR(COOH)_3$	* *Phæophorbin, Phytochlorin* $H_2R(COOH)_3$
* *Chlorophyllide* $MgR\left\{\begin{matrix}COOCH_3\\(COOH)_2\end{matrix}\right.$	* *Phæophorbide* $H_2R\left\{\begin{matrix}COOCH_3\\(COOH)_2\end{matrix}\right.$
* *Chlorophyll* $MgR\left\{\begin{matrix}COOCH_3\\COOC_{20}H_{39}\\COOH\end{matrix}\right.$	* *Phæophytin* $H_2R\left\{\begin{matrix}COOCH_3\\COOC_{20}H_{39}\\COOH\end{matrix}\right.$
Glaucophyllin, Rhodophyllin *Cyanophyllin, Erythrophyllin* $Mg.RH(COOH)_2$	*Glaucoporphorin, Rhodoporphorin* *Cyanoporphorin, Erythroporphorin* $H_2R.H.(COOH)_2$
Pyrrophyllin, Phyllophyllin $Mg.RH_2(COOH)$	*Pyrroporphorin, Phylloporphorin* $H_2RH_2(COOH)$
Ætiophyllin $MgRH_3$	*Ætioporphorin* H_2RH_3

Inspection of the above will show that ætiophyllin and ætioporphorin are the parent substances of the two groups; the other members are obtained from them by replacing hydrogen atoms by one, two, or three carboxyl radicles.

6. *The Decomposition of Chlorophyll by Alkali and by Acid.*

The action of alkali upon chlorophyll is twofold. Under certain conditions, a change in composition takes place; whilst under other conditions only rearrangements occur in the chlorophyll structure. In the present section, for the sake of clearness, the decompositions will be dealt with; and a full treatment of the intramolecular rearrangements will be deferred to the next section.

It will be remembered that when chlorophyll-*a* is submitted to the action of alkali at ordinary temperatures, the first change noted is the hydrolysis of the phytyl radicle. Thereafter, the methyl group is displaced in turn; and, finally, the salt of a tribasic acid, chlorophyllin-*a*, is produced. If, now, the temperature be raised to 140° C., carbon dioxide is split off and a dicarboxylic acid, glaucophyllin, is formed. At 165° C. in presence of alkali, this undergoes rearrangement into rhodophyllin, which is also a dibasic acid. Treated with alkali at 200° C., rhodophyllin in its turn loses carbon dioxide and yields a monocarboxylic acid, pyrrophyllin.[1]

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* Note that the third carboxyl group in these substances is masked by lactam formation. It has been shown free in the above formulæ merely for the sake of bringing out the analogies between the various compounds.

If hot alkali be allowed to act direct upon chlorophyllide-*a*, with no previous treatment in the cold, the decomposition takes a different but parallel course, owing to an intramolecular change occurring which produces iso-chlorophyllin-*a* instead of chlorophyllin-*a*. With alkali at 140° C. this isomeric substance yields cyanophyllin, isomeric with glaucophyllin. Cyanophyllin, when heated with alkali at 170° C., gives erythrophyllin. Finally, from erythrophyllin, alkali at 190° C. produces phyllophyllin.[2]

The table on opposite page will serve to bring out the parallelism between the various compounds formed in the latter stages of the two reactions.

Throughout these changes, the magnesium atom of chlorophyll retains its place in the molecule, as alkalis appear to have no power to displace it.

The action of acids upon chlorophyll, as was mentioned above, is to remove the magnesium from the molecule and replace it by two hydrogen atoms. Now it is clear that similar treatment might be given to the decomposition products of chlorophyll; and it is found that in their cases the same result follows. Thus for each magnesium-containing derivative there is a corresponding hydrogen compound.[3]

In this way we obtain from glaucophyllin the corresponding glaucoporphorin—

$$\underset{\text{Glaucophyllin.}}{\left[C_{31}H_{32}N_4Mg\right]\begin{matrix}COOH\\COOH\end{matrix}} \xrightarrow{\text{acid}} \underset{\text{Glaucoporphorin.}}{\left[C_{31}H_{34}N_4\right]\begin{matrix}COOH\\COOH\end{matrix}}$$

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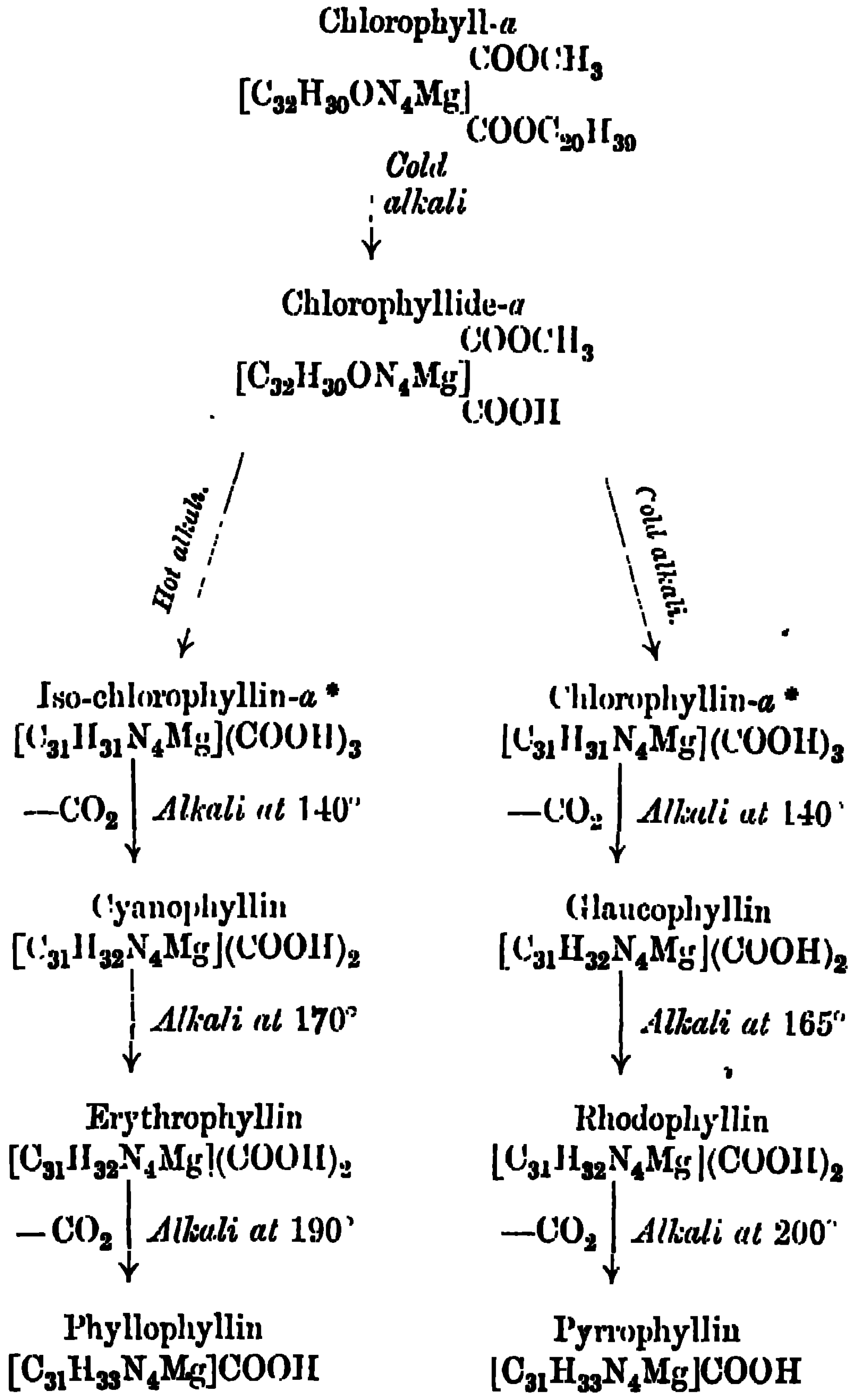
[1] Willstätter and Fritzsche, *Annalen*, 1909, **371**, 33; and Willstätter, *Ber.*, 1914, **47**, 2854.

[2] Willstätter, *Ber.*, 1914, **47**, 2854.

[3] Willstätter and Fritzsche, *Annalen*, 1909, **371**, 33.



Chlorophyll-*a*
$[C_{32}H_{30}ON_4Mg]\begin{matrix}COOCH_3\\COOC_{20}H_{39}\end{matrix}$
Cold alkali
Chlorophyllide-*a*
$[C_{32}H_{30}ON_4Mg]\begin{matrix}COOCH_3\\COOH\end{matrix}$
Hot alkali.
Cold alkali.
Iso-chlorophyllin-*a* *
$[C_{31}H_{31}N_4Mg](COOH)_3$
$-CO_2$
Alkali at 140°
Cyanophyllin
$[C_{31}H_{32}N_4Mg](COOH)_2$
Alkali at 170°
Erythrophyllin
$[C_{31}H_{32}N_4Mg](COOH)_2$
$-CO_2$
Alkali at 190°
Phyllophyllin
$[C_{31}H_{33}N_4Mg]COOH$
Chlorophyllin-*a* *
$[C_{31}H_{31}N_4Mg](COOH)_3$
$-CO_2$
Alkali at 140°
Glaucophyllin
$[C_{31}H_{32}N_4Mg](COOH)_2$
Alkali at 165°
Rhodophyllin
$[C_{31}H_{32}N_4Mg](COOH)_2$
$-CO_2$
Alkali at 200°
Pyrrophyllin
$[C_{31}H_{33}N_4Mg]COOH$

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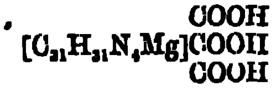
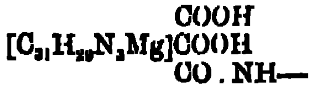
* As will be seen in the following section, chlorophyllin-*a* and iso-chlorophyllin-*a* probably contain lactam rings so that their formulæ may be written either as



$$[C_{31}H_{31}N_4Mg]\begin{matrix}COOH\\COOH\\COOH\end{matrix}$$

or



$$[C_{31}H_{29}N_3Mg]\begin{matrix}COOH\\COOH\\CO\,.\,NH—\end{matrix}$$

and in a similar manner we get rhodoporphorin from rhodophyllin, pyrroporphorin from pyrrophyllin and phylloporphorin from phyllophyllin.*

The final stage in the decomposition of chlorophyll requires more drastic reactions.[1] If the phyllins or porphorins are heated with soda-lime in a tube they lose carbon dioxide and are converted into substances containing no carboxyl radicles. When a phyllin is used as a starting-point, the substance produced is ætiophyllin, $C_{31}H_{34}N_4Mg$; whereas when a porphorin is treated with soda-lime it yields the corresponding magnesium-free compound ætioporphorin, $C_{31}H_{36}N_4$.

The decomposition of chlorophyll-*b* follows a slightly different course, some intermediate products being missing from the series, as can be seen from the table at the end of this volume.

7. *Intramolecular Changes in the Chlorophyll Nucleus.*

When chlorophyll-*a* is treated with cold alkali, both the methyl and phytyl radicles are removed by the hydrolysis and a substance known as chlorophyllin-*a* results. On the other hand, if hot alkali solutions are employed, the end-product is an isomeric compound iso-chlorophyllin-*a*.[2] The actual progress of the reaction is marked by a peculiar colour-change. When the alkali acts on chlorophyll (or on a chlorophyllide) the green tint of the substance alters to a deep brown and then, after a few minutes, the brown coloration vanishes and is replaced by the original green. The brown tint corresponds to the presence of what has been termed the "brown phase" of chlorophyll.[3]

Taking these facts together, the only possible explanation of them must be found in some kind of intramolecular change occurring in the chlorophyll molecule under the action of the alkali: and Willstätter has suggested that this change involves the lactam group which was postulated as one of the radicles in the chlorophyll nucleus.[4]

He assumes that at least three of the nitrogen atoms of chlorophyll are capable of taking part in lactam rings. Then, as there are three carboxyl radicles also present in the molecule, it can be see that a very considerable number of different lactams may be formed according to the choice which we make of the carboxyl group and the nitrogen atoms which are to build up the particular lactam in question.

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* See the table at the end of this volume.

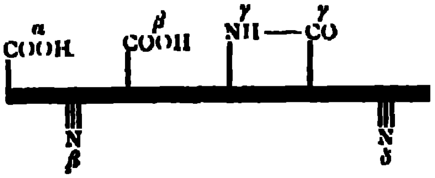
[1] Willstätter and Fischer, *Annalen*, 1913, **400**, 182.

[2] Willstätter, Fischer, and Forsén, *Annalen*, 1913, **400**, 147.

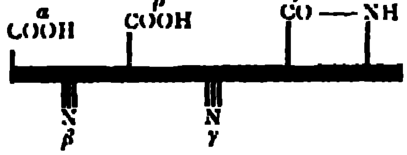
[3] Willstätter and Utzinger, *Annalen*, 1911, **382**, 129.

[4] *Ibid.*

Let us distinguish the three carboxyl radicles from one another by the letters α, β, and γ; and let us attach the symbols, β, γ, and δ to the nitrogen atoms which Willstätter assumes to take part in the reactions. The remainder of the chlorophyll nucleus may be represented by a heavy line. On this scheme, it is clear that we might have various isomeric compounds formed, each of which would contain a different type of lactam ring. Thus the γ-nitrogen atom might be linked with the γ-carboxyl group, as in (I.); or the γ-carboxyl group might change its mode of linkage and attach itself to the δ-nitrogen atom as in (II.).



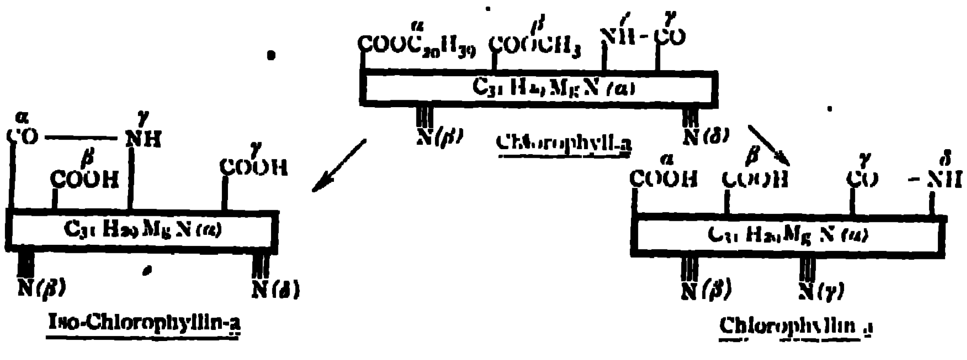
(I)



(II)

Now imagine that the compound (I.) is less stable than the compound (II.) owing to the difference in stability of the two lactam rings. It is clear that if the ring in (I.) be broken by any means it will not tend to re-form itself, but that, instead, the compound (II.) will be produced owing to the greater stability of its lactam ring.

Thus according to Willstätter's views, the formation of chlorophyllin-*a* and iso-chlorophyllin-*a* from chlorophyll may be represented in the following manner:—



This process of "allomerization," as Willstätter terms it, is obviously capable of application to the simpler chlorophyll derivatives as well as to chlorophyll itself; and when the complexity of the possible arrangements of the various carboxyl and imino radicles is taken into account it is no great wonder that three isomeric phytochlorins and an equal number of phytorhodins are known.

Both chlorophyll-*a* and chlorophyll-*b* give allomers simply on standing in alcoholic solution; which is sufficient to show how readily this intramolecular change takes place.

8. *The Magnesium Atom in the Chlorophyll Molecule.*

The part played by the magnesium atom in the structure of chlorophyll cannot be ignored if a true picture of the substance is to be obtained; yet it must be admitted that in some respects the problem which it presents is a thorny one.

From the fact that the magnesium atom remains as part of the structure of aetiophyllin, $C_{31}H_{34}N_4Mg$, it is clear that the metal must be attached to carbon or nitrogen; since all the oxygen has disappeared in the process of degradation to which the original chlorophyll has been submitted.

Now in all the magnesium-carbon compounds with which we are acquainted, the magnesium is easily removed by the action of water; it certainly cannot withstand the attack of alkali. Further, the nitrogen-magnesium bond also appears to be a weak one, if we may judge from the behaviour of magnesium methyl iodide with pyrrol.[1] Clearly the affinity which holds the magnesium atom to the chlorophyll nucleus is no ordinary bond; and we are left to conjecture its nature.

Willstätter[2] regards the metallic atom as forming a complex with the basic groups of the molecule. This question of "complex" formation is one of the debatable points in modern organic chemistry; and the fact that chlorophyll appears to be the first instance of magnesium acting in this manner will possibly not recommend the suggestion to some minds.* The problem is one which must be left to the judgment of the reader.

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[1] Hess and Wissing, *Ber.*, 1914, **47**, 1416.

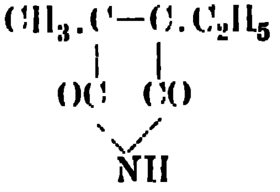
[2] Willstätter and Pfannenstiel, *Annalen*, 1908, **358**, 215; Willstätter and Fritzche, *ibid.*, 1910, **371**, 46.

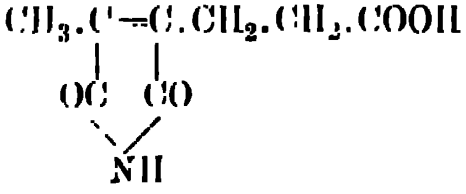
* The fact that the magnesium atom can be replaced by two hydrogen atoms without completely altering the character of the molecule makes the matter even more puzzling.

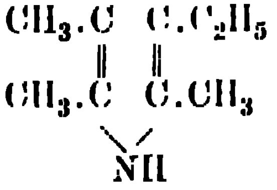
9. *The Structures of Ætiophyllin and Ætioporphorin.*

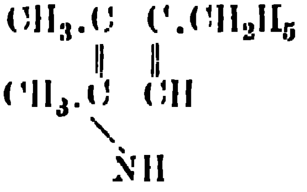
A consideration of the probable constitutions of the two ultimate degradation products in which the chlorophyll skeleton is retained leads us, as must frankly be admitted, into a region of almost pure hypothesis; but for the sake of completeness it is necessary to deal summarily with the subject.

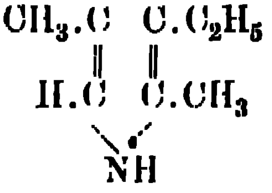
The actual facts at the disposal of the investigator are very few.[1] Oxidation of phylloporphorin produces more than one molecular quantity of methyl-ethyl-maleinimide (I.) along with one molecular quantity of hæmatic acid (II.). Reduction of porphorins leads to the formation of phyllopyrrol (III.), isohæmopyrrol (IV.), and cryptopyrrol (V.).


(I.)


(II.)


(III.)


(IV.)


(V.)

From these disjected members it is necessary to piece together the complete skeleton of the substance.

Willstätter's suggestions are as follows. From the nature of the above degradation products he assumes that the original substance must have contained four pyrrol nuclei. Now since the composition of ætioporphorin, $C_{31}H_{36}N_4$, contains a markedly low percentage of hydrogen, he concludes that the pyrrols must be so united and substituted that eight hydrogen atoms are left out as compared with the case in which the pyrrol groups are joined by single linkages. This saving of hydrogen atoms he proposes to accomplish by utilizing double bonds or calling ring formation to his assistance. Next he assumes a difference between pairs of pyrrol nuclei on the ground that two must be salt-forming radicles whilst the other two must be capable of complex formation. On this basis he suggests the following skeleton for the substance—

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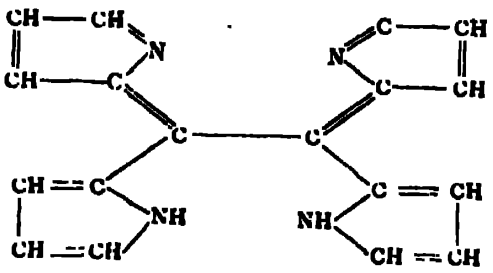
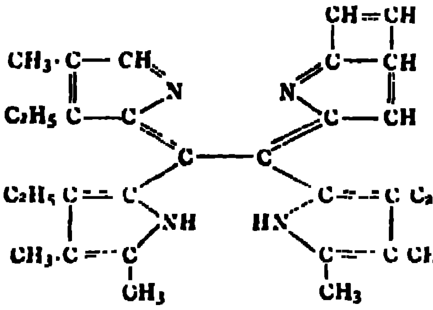
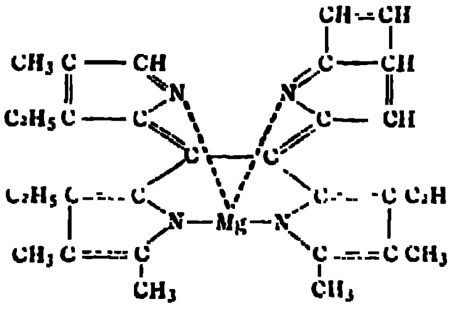
[1] Willstätter, *Ber.*, 1914, 47, 2831.



And from this, by substitution, he fills in the formulæ below for ætioporphorin and ætiophyllin :-



Aetioporphorin



Aetiophyllin

10. *The Relations between Chlorophyll and Hæmin.*

In the higher branches of the vegetable kingdom, chlorophyll plays a most important part in the vital economy of the organism; whilst in animals an equally essential factor is the colouring matter of the blood. The parallel functions of the two compounds suggested that some similarity in nature might be traced between chlorophyll and hæmin; and from this point of view a survey of the chlorophyll problem would be incomplete without a brief reference to the colouring material of blood.

Examination of the blood pigment shows that it is composed of two portions; an albuminous substance called globin and a non-albuminous compound named hæmatin. It is with the latter that we are here concerned.

Both chlorophyll and hæmatin are metallic derivatives, the magnesium of chlorophyll finding its analogue in the iron of hæmatin. In each case the metallic atom displays an abnormal character; and both compounds can be freed from their metallic portion by similar treatment. Finally, when analogous degradation methods are employed in the two cases, ætioporphorin is produced from both chlorophyll and hæmatin. These facts are sufficient to justify the assumption that the two substances are related to one another in a more than superficial degree.

When hæmatin is treated with hydrochloric acid it yields hæmin; and the reaction is supposed to take place by the replacement of a hydroxyl group by a chlorine atom—

$$R:Fe—OH \rightarrow R:Fe—Cl$$

Hæmin has recently been shown[1] to have the composition $C_{33}H_{32}O_4N_4FeCl$, which brings it into close resemblance with chlorophyllin. It will be seen that the divalent magnesium atom of chlorophyll is replaced by the divalent group: $=Fe—Cl$ in hæmin. Willstätter and Fischer[2] have brought forward a hæmin formula based to some extent upon their proposed structure for ætiophyllin. Küster,[3] on the other hand, rejects their suggestion and has put forward a formula of his own. It would require too much space to discuss the merits of either hypothesis, especially in view of the fact that both are quite possibly incorrect. In the present uncertain state of our knowledge, it is sufficient to indicate the general resemblance between chlorophyll and hæmin.

11. *Conclusion*

As chlorophyll is a more than usually complicated subject, it seems well in this place to summarize very briefly the undisputed information which has been acquired with regard to its constitution; for without such a summary the reader may feel that he is in the position of the man who "could not see the wood for the trees."

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[1] Willstätter and Fischer, *Zeitsch. physiol. Chem.*, 1913, **87**, 423.

[2] *Ibid.*

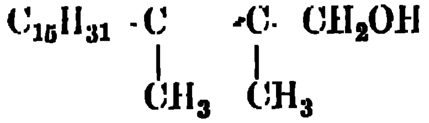
[3] Küster, *Zeitsch. physiol. Chem.*, 1913, **88**, 377.

Amorphous chlorophyll, extracted from leaves, is found to be a mixture of two compounds, chlorophyll-*a* and chlorophyll-*b*, both of which are methyl-phytyl esters. The compositions of the two compounds are :—

$$\left[\mathrm{C_{32}H_{30}ON_4Mg}\right]\begin{matrix}\mathrm{COOCH_3}\\ \mathrm{COOC_{20}H_{39}}\end{matrix}+\tfrac{1}{2}\mathrm{H_2O},\quad \left[\mathrm{C_{32}H_{28}O_2N_4Mg}\right]\begin{matrix}\mathrm{COOCH_3}\\ \mathrm{COOC_{20}H_{39}}\end{matrix}$$

Chlorophyll-*a*. Chlorophyll-*b*.

Phytyl alcohol has been shown to have the following structure :—



$$\mathrm{C_{15}H_{31}\cdot\underset{\underset{CH_3}{|}}{C}\quad \cdot\underset{\underset{CH_3}{|}}{C}\cdot\ CH_2OH}$$

When either of the chlorophylls is treated with acids, the magnesium atom is removed and its place is taken by two hydrogen atoms. The compounds thus formed are still methyl-phytyl esters; and they are termed phæophytins. After hydrolysis of the phytyl radicle, the residue is a methyl ester called a phæophorbide. The magnesium-free acids from which the esters are derived are named phæophorbins.

If either of the chlorophylls be acted on by cold dilute potash, the salt of a *tribasic* acid is formed, the acid itself being named a chlorophyllin. Hence, clearly, there is a third carboxyl radicle in the chlorophyll structure which is masked in some manner.

When the hydrolysis is carried out at higher temperatures in the case of chlorophyll-*a*, carbon dioxide in split off and two isomeric dicarboxylic acids, glaucophyllin and rhodophyllin, are formed; while by the use of still higher temperatures a further loss of carbon dioxide results in the production of a monobasic acid: pyrrophyllin.

Throughout these changes the magnesium atom is retained in the molecule; but by subsequent treatment with acids each of these decomposition products loses its magnesium, which is replaced by two atoms of hydrogen. In this way from glaucophyllin a substance named glaucoporphorin is obtained; and each of the other phyllins yields the corresponding magnesium-free porphorin. The decomposition of chlorophyll-*b* proceeds in an almost exactly similar manner, though certain of the intermediate compounds are missing in its series.

When the porphorins are heated with soda-lime, the last carboxyl group of the molecule is split off, and a substance ætioporphorin, $C_{31}H_{36}N_4$, is formed. The phyllins, when subjected to the same treatment, give the corresponding magnesium derivative ætiophyllin, $C_{31}H_{34}N_4Mg$.

The action of cold alkali solutions upon either chlorophyll-*a* or chlorophyll-*b* results, as has been said, in the production of a tribasic acid. This is found to be a mixture of two acids; so that from chlorophyll-*a* we get chlorophyllin-*a* and isochlorophyllin-*a*: and from chlorophyll-*b* two other isomeric chlorophyllin-*b* compounds are produced.

Further, when chlorophyll and its derivatives are treated with alkali they exhibit a peculiar colour change, turning from green to brown and back again—the so-called "brown phase" of chlorophyll.

The magnesium atom in the chlorophyll molecule is retained with a measure of affinity different from and greater than that which we are accustomed to find in organo-magnesium derivatives.

Finally, the nature of the ultimate degradation products of chlorophyll points to the probability that the chlorophyll molecule contains four pyrrol nuclei.

The foregoing summary contains all the important *facts* which have been established with regard to the structure of chlorophyll; and we must now deal with the theories which have been advanced to account for them.

The mystery of the third carboxyl group in the chlorophyll nucleus has suggested that this third carboxyl may be masked by lactam formation in which one of the nitrogen atoms of chlorophyll takes part. This view leads to the further hypothesis that, since there are three carboxyl groups and four nitrogen atoms present, a considerable number of possible lactam rings might be imagined, differing from one another in stability. Thus in one isomer it is assumed that the first carboxyl radicle forms a lactam with the first nitrogen atom; while in another isomer the first carboxyl reacts with, say, the second nitrogen atom to form a new lactam. On this hypothesis, the "brown phase" of chlorophyll represents the breaking of one lactam ring and the reclosing of the molecule into a more stable lactam grouping.

As to the structures proposed for ætiophyllin and ætioporphorin, their plausibility depends entirely upon the judgment of the reader; for it cannot be asserted that they have much solid basis; whilst as to the positions which the carboxyl groups of chlorophyll occupy in the ætiophyllin skeleton, not even the most random conjecture can be put forward with any justice.

CHAPTER IX

THE ANTHOCYANINS

1. *Introductory*

AN examination of plant pigments proves that they are, roughly, divisible into two classes. On the one hand we have the plastid pigments which are in some way intimately associated with the organized protoplasmic structure of the plant; whilst on the other hand we have soluble pigments, existing in solution in the sap of cells. These soluble pigments are termed anthocyanins.[1]

In view of the number and variety of the tints exhibited by flowers, it may appear that the term anthocyanin is a very loose one covering a multitude of colouring materials whose only relation with each other lies in the fact that they occur naturally in the sap of plants; but recent research has shown this idea to be erroneous. It seems practically established that the separate anthocyanins contain similar nuclei, no matter how much they may differ in colour from one another; and the wide variations of tint in flowers are to be ascribed to slight alterations in constitution which leave the main anthocyanin skeleton intact. Thus the anthocyanins may be regarded as a chemical class in the same way as it is customary to speak of the proteins, the carbohydrates, or the fats.

Although 250 years have passed since Boyle[2] published an investigation of the colour changes which take place when extracts from flowers are treated with acids and alkalis, it is only quite recently that much progress has been made in the study of the anthocyanin group.[3] The unstable nature of the compounds and the difficulty of preparing them in a pure state militated against research in this field. It was not until 1903 that an anthocyanin was first obtained in a crystalline condition by Griffiths.[1]

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[1] A complete account of the history of the anthocyanins as well as of their botanical significance is to be found in Miss Wheldale's book, *The Anthocyanin Pigments of Plants* (1916). For briefer accounts, see Everest, *Science Progress*, 1915, IX., 597, and Willstätter, *Ber.*, 1914, 47, 2831.

[2] Robert Boyle, *Experiments and Considerations Touching Colours*, 1664.

[3] A complete bibliography of the literature is to be found in Miss Wheldale's *Anthocyanin Pigments of Plants*, or in Perkin and Everest's *Natural Organic Colouring Matters.*

The next important stage in the history of the subject is marked by Grafe's discovery[2] that certain of the anthocyanins occurred in plants in the form of glucosides.

Meanwhile, on the botanical side of the problem a considerable amount of work had been carried out, chiefly dealing with the mode of formation of the anthocyanins in plants. Miss Wheldale[3] first suggested that anthocyanins might be formed from glucosides of the flavone or xanthone series by the action of oxidases; she indicated[4] that there are a certain number of anthocyanin types which give rise to a definite series of colour varieties.[5]

Having now surveyed the outlines of the anthocyanins' history from the chemical standpoint, it will be convenient, in the remainder of this chapter, to abandon the chronological method and deal with the present-day work in an order which will render the subject more readily comprehensible.

2. *The Methods of Extracting the Pigments from Flowers.*

The choice of a suitable raw material from which to extract flower pigments is the first step which must be taken; and here two alternatives present themselves, for either fresh flowers or dried petals might be selected as the best source of the required product. The anthocyanins, under certain conditions, are unstable substances; and from this point of view it might be thought best to work up fresh flowers rather than to risk the chance of decomposition taking place during the drying process. As against this, there are certain practical arguments. In the first place, plants are in flower only during a short period of the year and in certain definite localities; so that the choice of fresh flowers as a source of anthocyanins would entail the necessity of carrying out the extraction of the pigment at fixed times and places, and would demand the simultaneous collection of a very large number of flowers if any great quantity of raw material were required. Secondly, in fresh flowers the plant enzymes are still active, and their influence might make itself disagreeably marked in the course of the extraction. The substitution of dried petals for fresh flowers obviates both these difficulties, but on the other hand there is the possibility of a loss of anthocyanin owing to decomposition during the process of drying. Balancing one set of disadvantages against the other, it is found in practice better to employ the dried material than to use fresh flowers; and the extraction is generally carried out by using finely ground dried petals.

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[1] Griffiths, *Chem. News*, **89**, 249; *Ber.*, 1903, **36**, 3959.

[2] Grafe, *Sitzber. k. Akad. Wien.*, 1906, **115**, I., 975; 1909, **118**, I., 1033; 1911, **120**, I., 765.

[3] Miss Wheldale, *Proc. Phil. Soc. Camb.*, 1909, **15**, 137.

[4] *Ibid.*, *Proc. Roy. Soc.*, 1909, **81**, B, 44.

[5] Nierenstein and Miss Wheldale, *Ber.*, 1911, **44**, 3487.

The solvent chosen for the removal of the pigment from the petals of flowers or the skins of berries varies, of course, according to the nature of the anthocyanin present. In the case of the cornflower,[1] water alone suffices to dissolve the colouring material; hydrochloric acid in methyl alcohol solution is used in the cases of the rose,[2] the hollyhock,[3] the mallow,[4] the peony,[5] and the bilberry;[6] dilute alcohol is employed to remove the pigments from the larkspur[7] and the scarlet pelargonium;[8] whilst acetic acid is found to be the best solvent in the cases of the grape[9] and whortleberry.[10]

After the pigment has been obtained in solution it may be purified by one of three main methods[11]:—

1. Precipitation and crystallization of the chloride.
2. Purification by suitable reagents and crystallization of the chloride.
3. Separation in the form of a picrate and subsequent conversion into the chloride.

Under the first head come such cases as the precipitation of the chloride from alcoholic solution by means of ether.

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[1] Willstätter and Everest, *Annalen*, 1913, **401**, 189.
[2] Willstätter and Nolan, *ibid.*, 1915, **408**, 1.
[3] Willstätter and Martin, *ibid.*, 110.
[4] Willstätter and Mieg, *ibid.*, 122.
[5] Willstätter and Nolan, *ibid.*, 136.
[6] Willstatter and Zollinger, *ibid.*, 86.
[7] Willstätter and Mieg, *ibid.*, 61.
[8] Willstätter and Bolton, *ibid.*, 42.
[9] Willstätter and Zollinger, *ibid.*, 86.
[10] Willstätter and Mallison, *ibid.*, 15.
[11] *Ibid.*, 160.

Examples of the second category are to be found in the preparation of the cornflower pigment, which occurs as an alkali salt and can be purified by precipitating its aqueous solution with alcohol; and in the purification of the larkspur anthocyanin by heating it with dilute hydrochloric acid. In the picrate method the picrate is formed in the usual manner, purified, and then decomposed by a concentrated solution of hydrochloric acid in methyl alcohol.

3. *The Constitutions of Cyanin and Cyanidin.*

The pigment extracted from the cornflower is termed cyanin; and it is generally prepared in the form of its chloride, which is found to have the composition $C_{27}H_{31}O_{16}Cl$.[1] When this substance is heated for a few minutes with 20 per cent. hydrochloric acid, it is hydrolysed, yielding two molecules of glucose and one molecule of a crystalline substance which has been named cyanidin chloride[2]—

$$C_{27}H_{31}O_{16}Cl + 2H_2O = C_{15}H_{11}O_6Cl + 2C_6H_{12}O_6$$

Cyanin chloride. Cyanidin chloride. Glucose.

This reaction proves that cyanin is a diglucoside of the new body, cyanidin;[*] and, since glucose is colourless and cyanidin is coloured, this cyanidin forms the chromophoric portion of the pigment molecule.

The general structure of cyanidin has been established by its synthesis from quercetin,[3] and it may be well to give the complete synthetic process here, in order to show how cyanidin can actually be prepared from purely artificial materials.

In the Kostanecki synthesis[4] of quercetin (see scheme on p. 221), 2-hydroxy-4 : 6-dimethoxy-acetophenone (I.) is condensed with dimethoxyprotocatechuic aldehyde (II.) yielding 2′-hydroxy-4′ : 6′ : 3 : 4-tetramethoxychalkone (III.). On heating this for twenty-four hours with dilute hydrochloric acid, 1 : 3 : 3′ : 4-tetramethoxyflavonone (IV.) is produced. Treatment of this with amyl nitrite and hydrochloric acid converts it into the corresponding isonitroso-compound (V.), the methylene group next the carbonyl being attacked in the usual way. Hydrolysis of the isonitroso-compound splits off hydroxylamine, leaving a ketone (VI.); after which isomerization occurs by the production of the enolic form, resulting in the production of 1 : 3 : 3′ : 4′-tetramethoxyflavanol (VII.), which on demethylation with hydriodic acid yields quercetin (VIII.). When quercetin is reduced with sodium amalgam or magnesium in alcoholic solution containing hydrochloric acid and mercury, cyanidin chloride is formed, though the yield is very small. Apparently the reaction involves the formation of an intermediate product (IX.) which then loses a molecule of water, as shown in the scheme.

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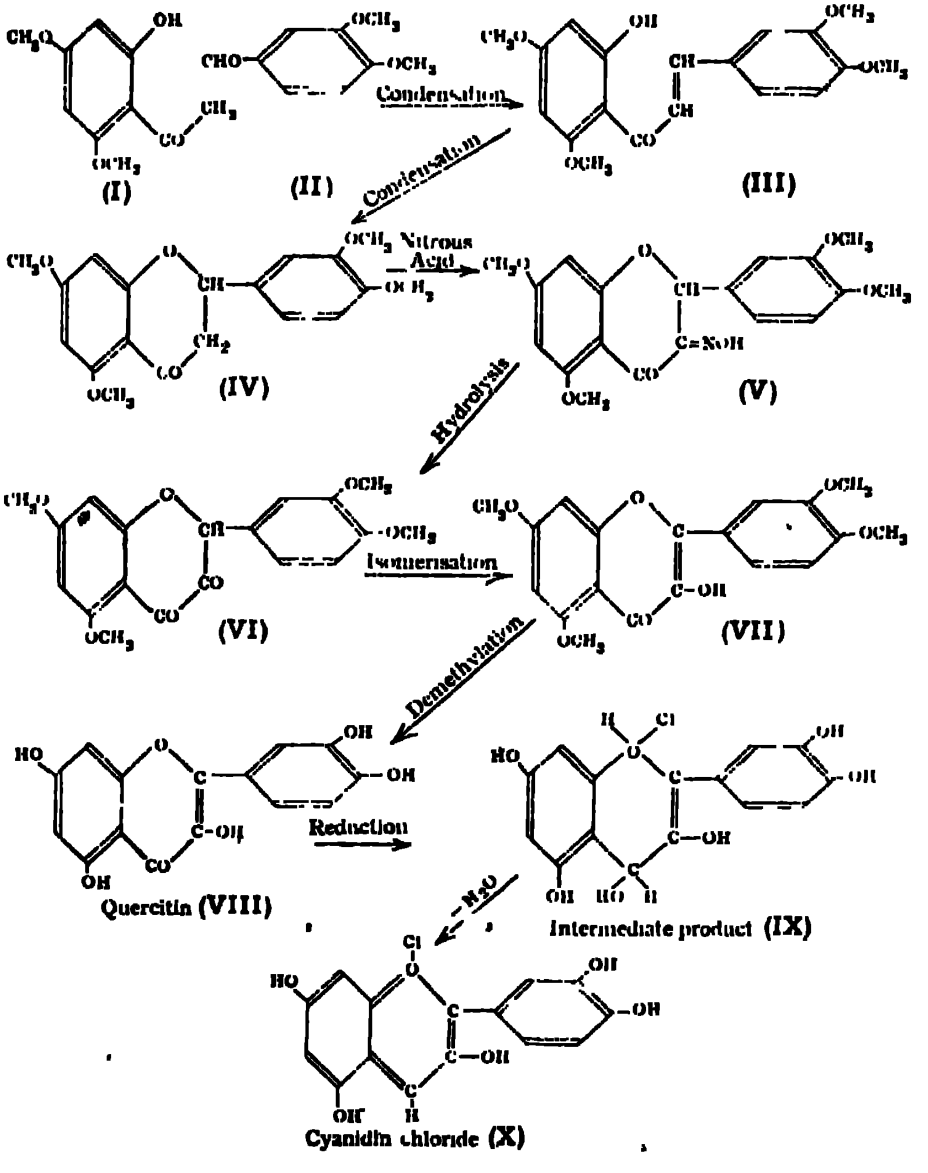
[1] Willstätter and Nolan, *Annalen*, 1914, **408**, 1.

[2] Willstätter and Everest, *Annalen*, 1913, **401**, 1.

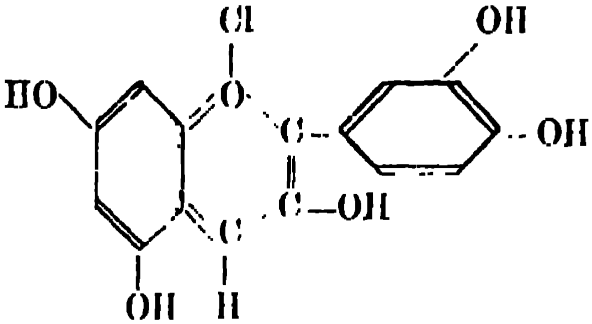
[*] From this is derived the class-name *anthocyanidins* to indicate the non-glucosidal portions of the anthocyanins.

[3] Willstätter and Mallison, *Sitzungsber. K. Akad. Wiss. Berlin*, 1914, 769.

[4] Kostanecki and Tambor, *Ber.*, 1904, **37**, 793; Kostanecki, Lampe, and Tambor, *ibid.*, 1402.



An examination of the formula ascribed to cyanidin chloride



will show that it contains a peculiar heterocyclic nucleus: the pyrylium system * which was discovered by Decker and Fellenberg.[1] The reason for assuming that this grouping is present lies in the consideration of the basic nature of the cyanidin molecule. Most of the oxonium salts, those of dimethylpyrone, for example, are susceptible to hydrolysis in aqueous solution; which points to the ordinary oxonium complex being weakly basic. Pyrylium compounds, on the other hand, are much more stable in solution than the commoner oxonium derivatives; and the behaviour of the cyanin salts in this respect tends to prove that they resemble pyrylium derivatives rather than such compounds as dimethylpyrone hydrochloride. The analysis of the cyanin salts also indicates that they are not akin to the normal oxonium hydrochloride, as they contain too little hydrogen to correspond with such a structure. On these grounds the pyrylium formula has been preferred.

From these facts it is clear that the anthocyanin cyanin is a diglucoside of cyanidin, which is a pyrylium derivative of the structure shown above.

4. *The Properties of Cyanin and Cyanidin Chlorides.*

The chloride of cyanin, when prepared in the usual manner, contains two and a half molecules of water of crystallization. Under the microscope, its rhombic leaflets appear tinted between grey-violet and brownish-yellow. In dilute solutions of sulphuric acid it appears red with a tinge of violet. It is very slightly soluble in cold water, alcohol, or dilute sulphuric acid; but is easily soluble in hot water and moderately soluble in 7 per cent. acid. When sodium carbonate is added to its solution, the colour becomes first violet and then blue. Its behaviour when its aqueous solutions are diluted is peculiar. The colour of the solution weakens much more rapidly than might be anticipated and the solution may eventually become colourless. The tint of the anthocyanin can be restored either by evaporating the solution or by adding a large excess of acid. It therefore seems reasonable to suppose that the case is one of hydrolytic dissociation accompanied by intramolecular rearrangement. With ferric chloride, cyanin gives a blue tint in alcoholic solutions and a violet tinge in aqueous solutions;[1] whilst with lead acetate it gives a characteristic lead salt.[2]

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* This is what Collie termed "oxene." See p. 254.

[1] Decker and Fellenberg, *Annalen*, 1908, 364, 1.

Turning now to cyanidin, it is found to crystallize with one molecule of water, which is retained with extraordinary tenacity. It is a brownish-red substance giving, when dissolved in dilute acids or alcohol, a red solution with a tinge of violet. Insoluble in water, it is readily soluble in alcohols; very slightly soluble in dilute hydrochloric acid but comparatively soluble in 7 per cent. sulphuric acid. With sodium carbonate it gives the same colour change as cyanin, turning first to blue and then to violet. The hydrolytic dissociation of cyanidin is much more marked than that of its parent anthocyanin; for when hot water is added to its alcoholic solution a violet precipitate is produced. The reaction with ferric chloride is slightly different also; for in alcohol a stable blue coloration is produced by cyanidin; whereas in aqueous alcoholic solution only an unstable violet tint is observed.[3] As in the case of cyanin, lead acetate yields a characteristic salt of cyanidin.[4]

The nature of the colourless modifications which are obtained by hydrolytic dissociation from both cyanin and cyanidin is not very clearly understood. In the case of cyanin chloride, it is found[5] that decolorization takes place when the chloride is heated for a short time in dilute alcohol at 80° C. The decolorized substance has properties resembling those of a yellow flavonol pigment; it is soluble in ether; colourless in acid solution, yellow in alkaline solution; from acid solutions it can be extracted with ether, from which it can be removed by shaking with alkali. On boiling with acids the colourless variety is reconverted into the ordinary coloured cyanidin salt.

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[1] Willstätter and Mieg, *Annalen*, 1915, **408**, 124

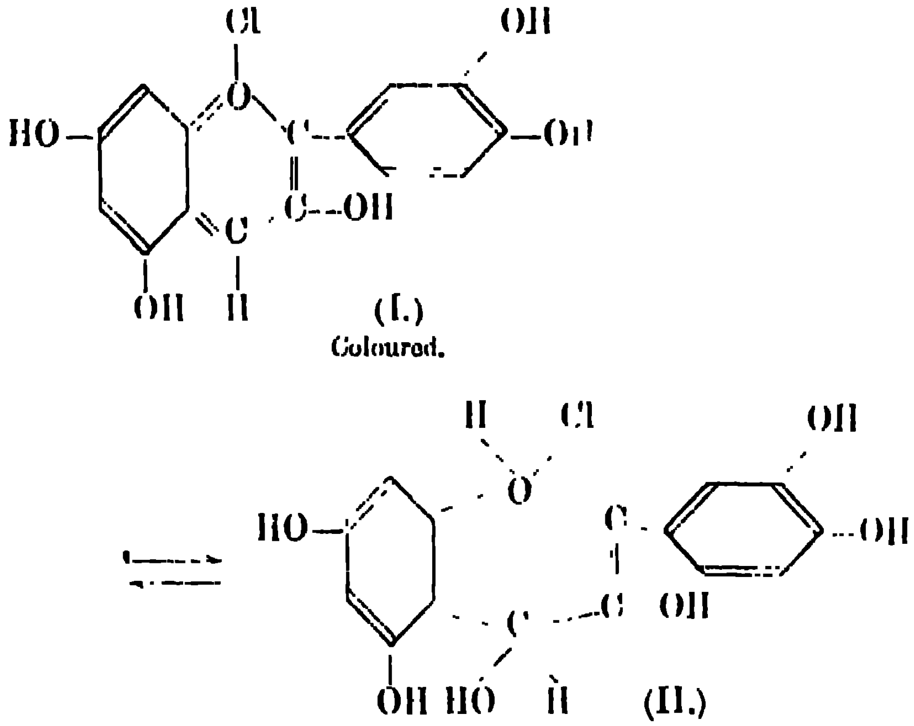
[2] Willstätter and Everest, *Annalen*, 1913, **401**, 225.

[3] Willstätter and Mieg, *Annalen*, 1915, **408**, 125.

[4] Willstätter and Everest, *Annalen*, 1913, **401**, 229.

[5] Everest, *Proc. Roy. Soc.*, 1914, **87**, B., 444.

Everest[1] suggests that cyanin chloride exists in solution as an equilibrium mixture of (I.)[*] and (II.), and that one set of conditions favours the stability of (I.), whilst under other conditions (II.) is the more stable form.



(I.)
Coloured.

(II.)
Colourless.

A distinction between anthocyanins and the corresponding anthocyanidins is found in the fact that amyl alcohol does not extract the former from acid solutions; but if the solution be heated so as to hydrolyse the anthocyanins to anthocyanidin, the latter passes into amyl alcohol readily.[2]

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[1] Everest, *Proc. Roy. Soc.*, 1914, **87**, B., 444.

[*] The glucose molecules are omitted from the formulæ.

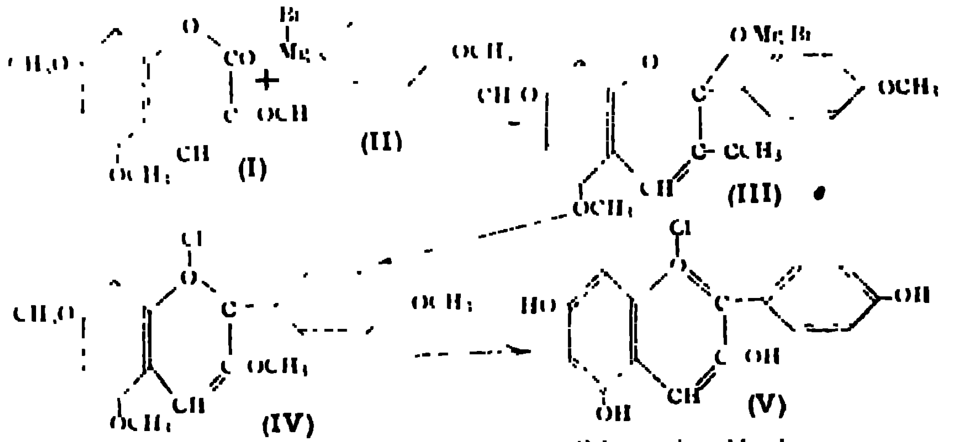
[2] Willstatter and Everest, *Annalen*, 1913, **401**, 205.

5. *The Synthesis of Pelargonidin.*

The flowers of the scarlet pelargonium are found to contain an anthocyanin which has been named pelargonin. This substance when isolated in the form of its chloride is shown to have the composition $C_{27}H_{31}O_{15}Cl$, and to contain, in addition, four molecules of water of crystallization.

On hydrolysis it proves to be a glucoside, and yields two molecules of glucose and one molecule of a substance pelargonidin chloride, akin to cyanidin chloride, and having the composition $C_{15}H_{11}O_5Cl$ with one molecule of water of crystallization.

Pelargonidin[1] has recently been synthesized in the following manner: 3 : 5 : 7-trimethoxycoumarin (I.) is allowed to interact with magnesium anisyl bromide (II.). When the intermediate compound (III.) is hydrolysed with hydrochloric acid it yields anisyltrimethoxyphenopyrylium chloride (IV.) which, after demethylation with hydriodic acid and treatment with hydrochloric acid, produces a substance (V.), indistinguishable chemically or spectroscopically from natural pelargonidin—



Pelargonidin chloride

6. *The Constitutions of Delphinin and Delphinidin.*

The anthocyanin of the larkspur is termed delphinin[2] and with it a slightly more complex field is entered. A glance at the formula of delphinin chloride: $C_{41}H_{39}O_{21}Cl$, shows that it has a molecular weight of 902 as compared with 646 for cyanin chloride; so it is evident that the former substance must contain some heavy radicle in addition to those found in cyanin or pelargonin.

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[1] Willstätter and Zechmeister, *Sitzungsber. K. Akad. Wiss. Berlin*, 1914, 886.

[2] Willstätter and Mieg. *Annalen*, 1915, **408**, 61.

Hydrolysis of delphinin proves the correctness of this. In addition to the products which might be expected (glucose and delphinidin) two molecules of *p*-hydroxybenzoic acid make their appearance; so that the equation for the reaction may be written thus—

$$\begin{array}{ccccccc} C_{41}H_{39}O_{21}Cl + 4H_2O & = & 2C_6H_{12}O_6 & + & 2HO.C_6H_4.COOH & + & C_{15}H_{11}O_7Cl \\ \text{Delphinin chloride.} & & \text{Glucose.} & & p\text{-Hydroxybenzoic acid.} & & \text{Delphinidin chloride.} \end{array}$$

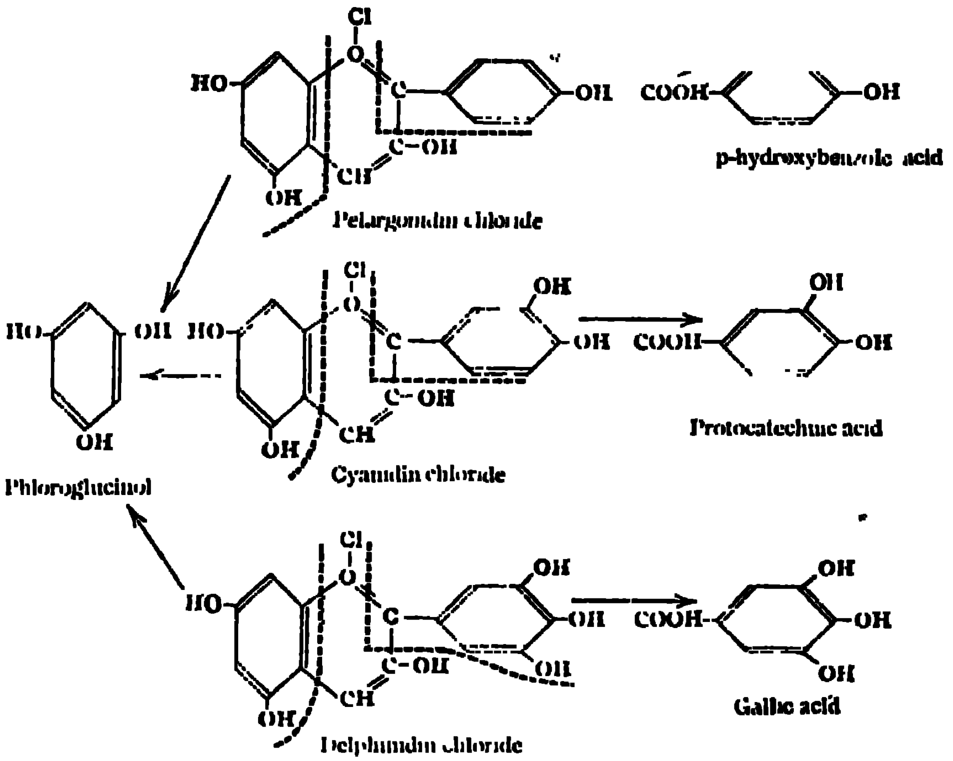
It appears from this that delphinin, like the other anthocyanins, is a glucoside; but that two of its hydroxyl radicles are esterified with *p*-hydroxybenzoic acid. Which of the hydroxyl groups are thus affected is not known definitely; but by analogy with populin (benzoylsalicin) it is assumed that the benzoylation takes place in the glucose chain and not in the delphinidin portion of the molecule.

The next stage in the deduction of delphinin's constitution is made by comparing the formulæ of pelargonidin, cyanidin, and delphinidin chlorides:

Pelargonidin chloride	$C_{15}H_{11}O_5Cl$	or	$C_{15}H_7OCl(OH)_4$
Cyanidin chloride	$C_{15}H_{11}O_6Cl$	or	$C_{15}H_6OCl(OH)_5$
Delphinidin chloride	$C_{15}H_{11}O_7Cl$	or	$C_{15}H_5OCl(OH)_6$?

The comparison suggests that the difference between cyanidin and delphinidin may lie in the presence of an extra hydroxyl group in the delphinidin molecule.

Confirmation of this view is obtained when the results of heating the three compounds with alkali are considered. All three yield phloroglucinol; so that they contain a common grouping. In addition to the trihydric phenol, however, pelargonidin yields *p*-hydroxybenzoic acid; cyanidin produces protocatechuic acid; whilst delphinidin gives rise to gallic acid. From this it appears a reasonable deduction that the portion of the molecule which produces *p*-hydroxybenzoic acid in the case of pelargonidin is the same in nature as that which gives rise to gallic acid from delphinidin. A comparison between the two established formulæ and the one suggested for delphinidin will make the matter clear:—



7. *Other Anthocyanins.*

Mention must now be made of some other plant pigments which contain the skeletons we have already described, though the details of their structures have not yet been entirely cleared up.

Pelargonidin forms the basis of the antocyanin of the flowers of the plant *Salvia coccinea*. This anthocyanin is called salvianin; and on hydrolysis it yields pelargonidin, two molecules of dextrose, and a considerable quantity of malonic acid. It is therefore more complex in its structure than the usual flower pigment.[1]

In the summer aster occurs an anthocyanin, callistephin, which on hydrolysis produces pelargonidin and one molecule of dextrose.[2] The same flowers yield a second anthocyanin, asterin, which hydrolyses into cyanidin and dextrose.[3]

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[1] Willstätter and Bolton, *Annalen*, 1916, **412**, 113.

[2] Willstätter and Burdick, *Annalen*, 1916, **412**, 149.

[3] *Ibid.*

The anthocyanin of the winter aster is chrysanthemin, derived from dextrose and cyanidin. Cyanidin also forms the foundation for the colours of *Zinnia elegans*, *Gaillardia bicolor*, *Helenium autumnale*, *Gladiolus Tulipa Gesneriana*, *Tropæolum majus*, *Rubes rubrum*, the raspberry, and the berry of the mountain ash.[1] The cherry contains keracyanin, built up from cyanidin, dextrose, and rhamnose; whilst the sloe owes its colour to prunicyanin, which is formed from cyanidin, rhamnose, and some as yet unidentified hexose.[2] The plum also contains a cyanidin glucoside.[3]

Peonin, the anthocyanin of the peony, belongs to the cyanidin series. It is a diglucoside of peonidin, which appears to be a methyl derivative of cyanidin in which the methyl radicle replaces a hydrogen atom of one of the hydroxyl groups.[4] Another cyanidin derivative is idaein,[5] the anthocyanin of the whortleberry. It differs from the usual type of anthocyanin in that it is a galactoside and not a glucoside.

The poppy[6] contains two anthocyanins, one of them, mecocyanin, being a cyanidin derivative, whilst the other resembles the glucosides of delphinidin.

Turning to delphinidin derivatives, it is found that the pansy owes its colour to the anthocyanin violanin,[7] which on hydrolysis yields delphinidin, rhamnose, and some as yet unidentified hexose, though these three products do not occur in equimolecular quantities in the reaction mixture. Monomethyl ethers of delphinidin are found in myrtillin,[8] the anthocyanin of bilberries, and petunin,[9] the anthocyanin of petunias. Dimethyl ethers of delphinidin have been isolated from oenin,[10] the anthocyanin of grapes, and from malvin,[11] the anthocyanin of the wild mallow.

Finally, mention may be made of a glucoside ampelosin, which occurs in the wild vine. Its constitution has not yet been determined.

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[1] Willstätter and Bolton, *Annalen*, 1916, **412**, 136.

[2] Willstätter and Zollinger, *Annalen*, 1916, **412**, 164.

[3] *Ibid.*

[4] Willstätter and Nolan, *Annalen*, 1915, **408**, 136.

[5] Willstätter and Mallison, *Annalen*, 1915, **408**, 15.

[6] Willstätter and Weil, *Annalen*, 1916, **412**, 231.

[7] *Ibid.*, 178.

[8] Willstätter and Zollinger, *Annalen*, 1915, **408**, 83.

[9] Willstätter and Burdick, *Annalen*, 1916, **412**, 217.

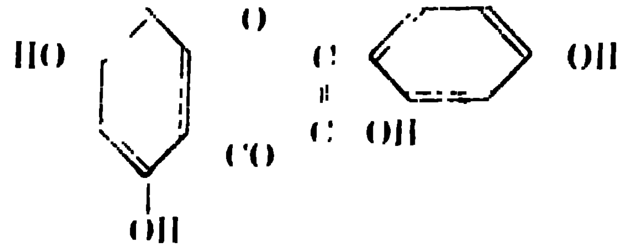
[10] Willstätter and Zollinger, *Annalen*, 1915, **408**, 83.

[11] Willstätter and Mieg, *Annalen*, 1915, **408**, 122.

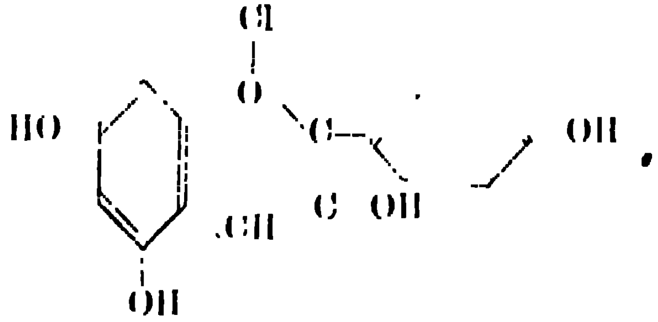
8. *The Anthocyanins and the Flavones.*

It may be of interest to point out the similarity in structure which can be traced between the flower pigments and the natural dyes occurring in plants; for the close resemblance in the skeletons of the two classes may throw light in the future upon the mode in which both types are built up within the organism. Such a similarity can hardly be regarded as due to mere chance.

Taking kampherol as a flavone representative, and comparing it with pelargonidin chloride as a typical example of the anthocyanins, it will be seen that they bear a striking resemblance to one another in general structure:—



Kampherol.



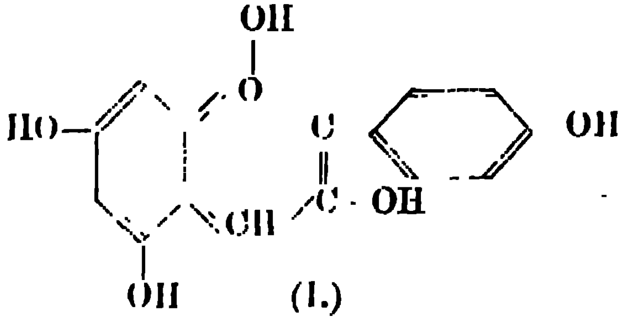
Pelargonidin chloride

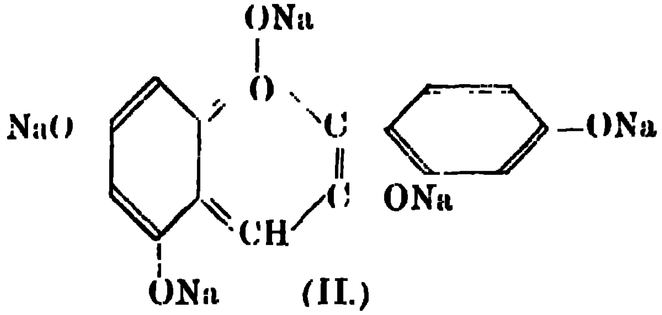
The only difference between them is to be found in the heterocyclic nucleus; the one is a true pyrone, whilst the other contains a —CH= group instead of the carbonyl radicle; and its structure is therefore more benzenoid in character. This difference is, of course, exhibited in their salts; the kampherol salts, being derived from a true pyrone, are easily hydrolysed even in the sap of plants; whilst the salts of anthocyanins are sufficiently stable to exist without decomposition in the vegetable structure.

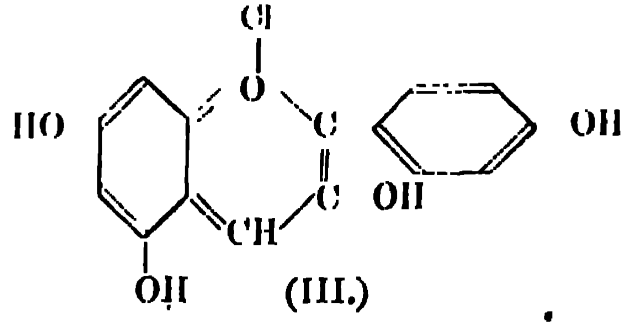
9. *The Origin of Colour Variation in Plants.*

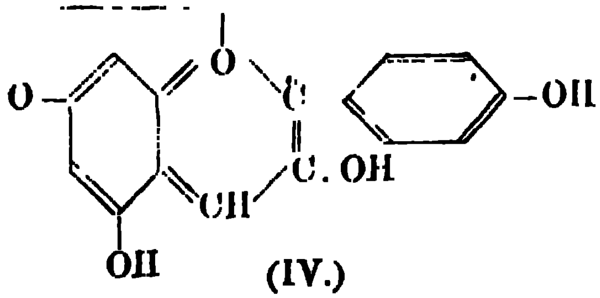
In view of the strong family resemblance between the various plant pigments, it may be interesting to indicate the manner in which such closely related compounds might give rise to such gradations of tint as are shown in the flowers.

An examination of the structure of pelargonidin will show that it is capable of yielding various types of derivatives: metallic salts like (II.), oxonium salts like (III.), and internal ethers like (IV.):—


(I.)


(II.)


(III.)

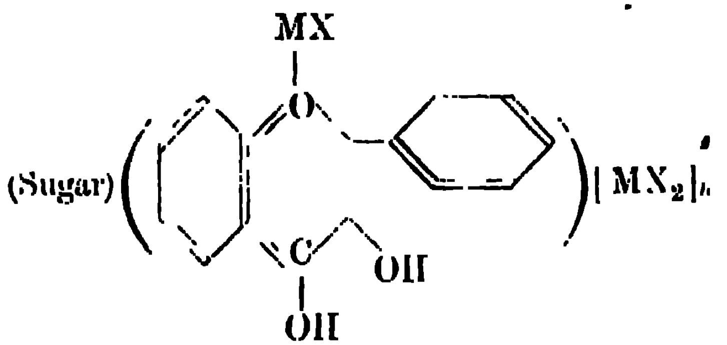

(IV.)

The importance of metallic derivatives of the anthocyanins has been emphasized by recent work on the subject.[1] Reduction of a flavone derivative by means of a metal and a *mineral* acid leads to a production of a red compound; but when magnesium and an *organic* acid such as acetic acid is employed in presence of mercury, the colour of the product is found to diverge from the normal red tint. Thus when myricetin (I.) is reduced in this way, it yields green compounds which have the composition $C_{18}H_{11}O_8 . Mg . OAc, [Mg(OAc)_2]_n$. The reaction apparently proceeds in stages. In the first stage, the phenopyrylium derivative (II.) is formed; which then passes by elimination of acetic acid into (III.), which finally unites with magnesium acetate to produce (IV.) (see p. 232).

If, instead of myricetin itself, a rhamnoside derivative, myricitrin, is used, the resulting product is a deep blue substance containing four molecules of magnesium acetate.

The difference between the reaction-products when mineral and organic acids are employed has been traced to the fact that the radicle —Mg.Cl is replaced by a chlorine atom if hydrochloric acid is present in quantity; so that the end-product is the red oxonium chloride.

Basing themselves upon these results, Shibata, Shibata and Kasiwagi suggest that metallic complex salts of the type—



are important factors in flower coloration and give rise to the "blue" anthocyanins. The metallic atoms which they contain (indicated by M in the formula) are probably calcium and magnesium. The "violet" and "red" pigments are assumed to be complex salts containing fewer hydroxyl groups than the "blue" ones; or to be mixtures of the "blue" compounds

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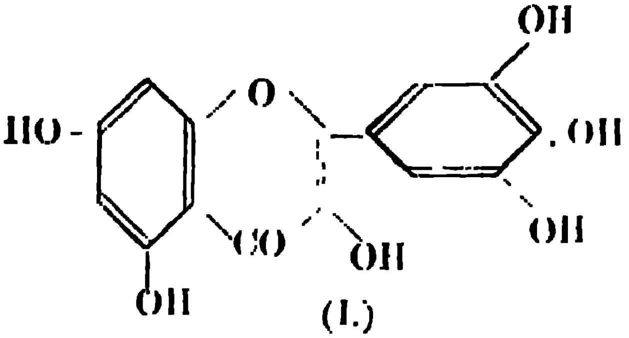
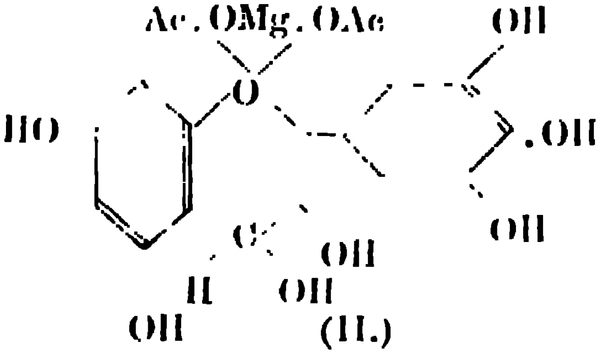
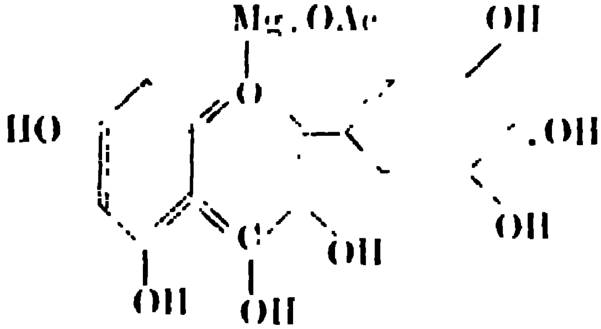
[1] Shibata, Shibata and Kasiwagi, *J. Amer. Chem. Soc.*, 1919, **41**, 208.


OH
HO
O
.OH
CO
OH
OH
OH

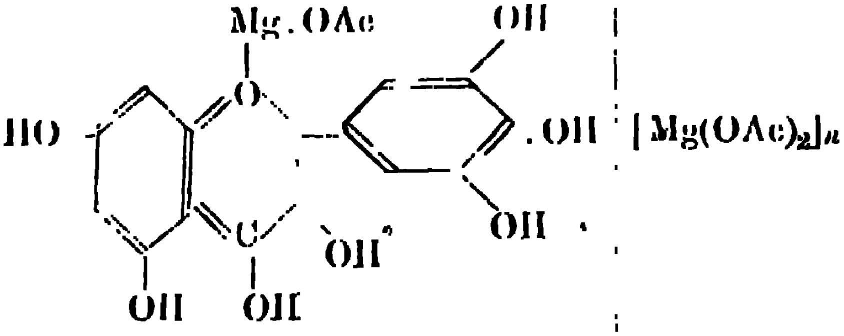
(I.)


Ac.OMg.OAc
OH
HO
O
.OH
C
OH
H
OH
OH
OH

(II.)


Mg.OAc
OH
HO
O
.OH
C
OH
OH
OH
OH

(III.)


Mg.OAc
OH
HO
O
.OH
[Mg(OAc)2]n
C
OH
OH
OH
OH

(IV.)

with a certain quantity of the red oxonium salts which have been formed from the "blue" derivatives by decomposition with acids.

The existence of these various types would be conditioned by the nature of the sap in the neighbourhood of the pigment; and as the sap must obviously be more highly concentrated the nearer we go to the evaporating surface of the petals, it is evident that variations in the structure of the pigment must be expected. Again, the sap in certain parts of the plant may be more alkaline than in others; and as the cyanidins are indicators, it is clear that their tint will be affected by this factor also.

CHAPTER X

SOME THEORIES OF THE NATURAL SYNTHESES OF VITAL PRODUCTS *

1. *Introductory*

WHEN we survey that portion of organic chemistry which deals with compounds derived from natural sources, it is impossible to overlook the fact that, although we can synthesize many of these substances in our laboratories, the methods which we employ there differ entirely from those which are utilized in the natural production of the same substances by physiological or phytological means.

The first great difference between the lines of syntheses is found in the ranges of temperature employed in the two cases. In the plant or in the animal body, the reactions which build up extremely complicated products take place, obviously, within very narrow temperature limits; whilst in our laboratories we employ conditions varying from one another by as much as 300° C. Not only so, but we press into our service reagents of such instability and reactive power that it is impossible to conceive their coming into existence at all in the animal or vegetable kingdom.

It may be argued that this is only natural. After all, our object in laboratory practice is to obtain the best yield in the shortest time; and a resort to natural methods may be regarded with the same distaste as might be shown by a traveller from London to Inverness at the suggestion that he should tear up his first-class railway ticket and perform his journey on foot. But on the other side there is something to be said also. Very little is as yet known with regard to vital syntheses; and it is quite possible that the methods adopted by the living machine, when we come to understand them, may be simpler and more efficient than our present-day laboratory reactions. Even if this view proves to be erroneous, there can be no doubt that attempts to throw light upon plant and animal methods will broaden our outlook upon organic chemistry as a whole; for at present organic chemists, almost without exception, leave this branch of the subject severely alone.

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* When this chapter was under consideration, Professor Collie, at my request, sent me a communication embodying some of his views on the subject; and these appeared to me to necessitate the re-writing of the major part of the chapter on the basis of his notes. To avoid continual reference to this private communication and at the same time to indicate his share in the matter, I have placed a † at the beginning of each paragraph which is derived from his notes.—A. W. S.

† One reason for this abstention is perhaps to be found in the manner in which our chemical literature is compiled. In the textbooks of the subject, the naturally occurring substances are not grouped according to their place of origin but are arranged under the headings of alcohols, acids, etc., and are scattered about the literature merely to fill up gaps in long lists of artificially prepared compounds.[1] Organic chemistry of to-day is not properly organic chemistry at all, but has swollen into a chemistry of thousands of carbon compounds which do not occur in nature. Many of these synthetic compounds are the result of the immense industry of chemists who have been misled by the idea that a new compound must necessarily be interesting; and also of the very narrow outlook of certain other chemists who think that a graphic formula is the be-all and end-all of the science.

† Of course the chief reason why in textbooks we find so little information about "how" and "why" certain compounds are produced in plants and animals is because we do not know the answers to the questions involved. In the plant, for example, there appears to be no step-by-step process for making more and more complex materials, as we do in the laboratory. Carbon dioxide, water, and nitrogen, combined or otherwise, are absorbed by the green plant in sunlight. The first substances which can be isolated from the reaction products are sugars, the next ones are the highly complex starches, celluloses, and proteins. All the organic compounds

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[1] Haas and Hill's *Chemistry of Plant Products* (1917) gives an excellent survey of the "organic" field, and should be consulted by anyone who desires to go further into the subject.

such as acids, esters, fats, colouring matters, and alkaloids are most probably formed by a down-grade process: a decomposition of the starches, celluloses, and proteins. The chemist in his laboratory seeks to make these compounds by syntheses from simpler bodies; the plant appears to produce them by a reverse operation from stored-up material of an extremely complex molecular structure.

† Some of these down-grade processes can be followed to a certain extent in the laboratory. Celluloses, starches, and proteins can be hydrolysed, oxidized or otherwise decomposed. But our methods, as a rule, are too violent; and the fine grades of reaction which take place slowly at ordinary temperatures in plants have, up to the present, defied imitation in the laboratory.

† Nevertheless, we must not lose sight of the fact that although natural reactions often *seem* to operate in a way quite different from laboratory reactions, yet both sets must obey the same laws. Therefore, if we find that in the synthetic processes of our laboratories certain lines are followed under conditions which could exist in plants, we are not far wrong in assuming that, in the down-grade processes of nature, the same general direction will be taken in the formation of products.

† Another point arises here. All reactions which are likely to be employed in vital syntheses are reversible; and hence if they be carried out in glass test-tubes they must come to an equilibrium point, except in those cases wherein gaseous products are formed. How, then, does the plant succeed in producing its high yields of certain substances which, in a test-tube, would be formed only in minor quantities from the same reagents? When we examine the living plant, we are at once struck by the wonderful mechanism of the natural chemical laboratory which we find there. It is a system of test-tubes made of cellulose and differing from ordinary test-tubes in that the walls are constructed from semi-permeable membranes. Each cellulose test-tube is immersed in a solution differing from that which is contained within the cellulose vessel. The membrane acts not only as a container, as the glass test-tube does, but in addition it behaves as a filter, a concentrator, or a separator. Thus during the progress of a down-grade reaction in which a complex molecule is broken up into

constituent parts, the cellulose wall permits a certain product to accumulate in one part of the plant whilst a mixture of other compounds may be withdrawn to a different region. In this way the ordinary equilibrium stage of the reaction is evaded; and much higher yields may thus be attained.

† But what starts this down-grade process? Once the plant has synthesized its starches, etc., why are these substances not stable, as they are when we place them in bottles in a chemical museum? To answer this question we must know how the plant grows; and what is meant by a living material as opposed to dead matter. The differences between the two are much too marked to allow of dispute.

† When a crystal grows in a solution, we may regard the process as the first glimmering of individual life in that particular substance. Infinitely more complex is the growth of protoplasm from carbon, hydrogen, nitrogen, and oxygen; the smallest particle of protoplasm is inconceivably greater than the atoms from which it has been built up. Still more complex is the growth of a plant from the seed. In all these cases a directive agency seems to be at work. Whether further investigation will or will not show that all these phenomena can be explained by purely chemical and physical laws, time alone can show; but it is quite certain that at present the only scientific course is to admit that we do not know. The chemical reactions which take place in the living plant are in certain respects so different from those which go on in the laboratory that we are forced to recognize the action of some subtle agency which, up to the present, we have been unable to imitate.

† Let us return to the degradation of the starches, celluloses, and proteins. The plant, under the action of sunlight, has stored these substances in its body and has grown to its full size. The directive force begins to get exhausted; the plant is growing old; most of its starches are now used up; and the celluloses and proteins are beginning to undergo more and more rapid decomposition. The down-grade process has set in with increasing velocity. The plant is still alive, but the system is losing instead of gaining energy. Fermentations have begun; but fermentations will only explain a part of the process, for they are catalytic reactions which would,

normally, reach their equilibrium stages whether the plant were young or old. The enzymes causing them are chemical reagents which enable part of the stored-up energy in the plant to be set free again; but the actual disturbance of equilibrium is due to the separation and segregation of the reaction products by the semi-permeable membranes.

It seems not impossible that the later stages in the life-history of a plant are brought about by some change in the nature of its cell-walls, akin, perhaps, to the ossification of arteries which sets in within the animal body under somewhat similar conditions. If, at this stage, the cells ceased to act as semi-permeable membranes, the whole machinery of the plant would become choked with by-products, and the natural changes which are necessary in living matter would gradually come to an end.

† During the growing phase of the plant, starches, cellulose, proteins, and enzymes are produced; but as the plant ages the growing energy lessens, the enzymes get the upper hand and prey upon the substance of the plant. They are the parasites which finally kill their parent.

† Considering the importance of the ferments in the scheme of nature, it is extraordinary to notice how very briefly they are referred to in most textbooks of organic chemistry;[1] and the textbook reflects to a great extent the outlook of the average organic chemist. It is hardly to be wondered at if the new generation of organic chemists, trained by such methods, becomes imbued with an almost superstitious reverence for the deluge of organic compounds which have been spawned in thousands in chemical laboratories for, apparently, no useful purpose whatever.

2. *The General Course of Vital Syntheses and Degradations.*

† When the action of the living machine is considered in its broadest aspects, there seems to be no doubt that it can be regarded as divisible into two opposed processes. In the first group come the synthetic reactions by means of which the products assimilated by the plant or animal are converted into

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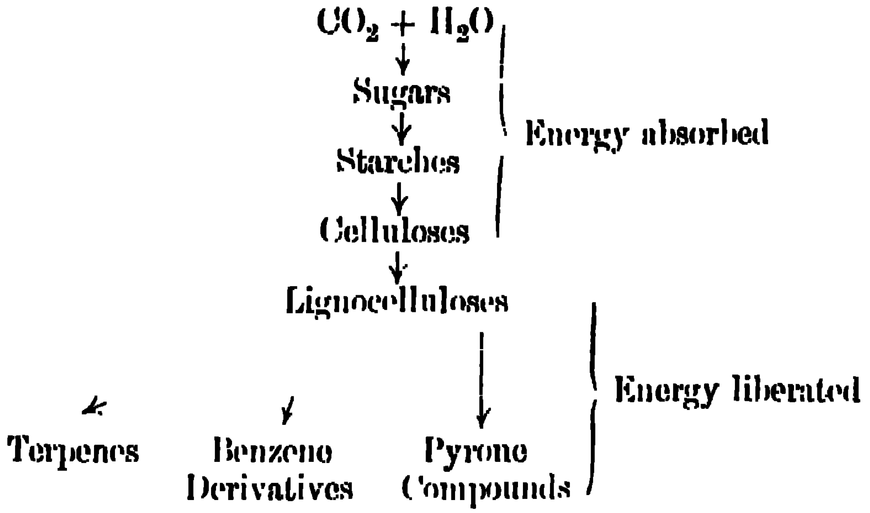
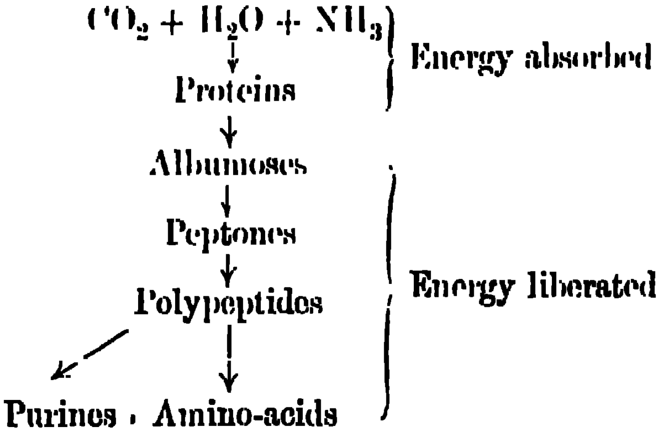
[1] Haas and Hill, in their *Chemistry of Plant Products*, give a very good summary of the nature of enzymes and their action in plants.

extremely complicated celluloses and proteins; whilst in the second class are placed those decompositions and changes which convert the celluloses and proteins into simpler substances The first series of reactions are probably carried on with the absorption of external energy; the second group comprises reactions which liberate this energy once more. It may be convenient at this point to give a table indicating the course of vital action in the two cases:—





In the case of the cellulose synthesis, it seems evident that the reaction leads to the formation of long chains built up from sugar molecules; for hydrolysis of the cellulose yields simple carbohydrate derivatives almost unaltered. Thus in this case the reaction is quite uncomplicated and appears to be simple dehydration or polymerization.

The transformation of the celluloses into lignocelluloses is evidently more complex, as the latter compounds appear to contain cyclic nuclei of various types; and from them the aromatic and heterocyclic substances formed in plants may be produced by a series of degradation reactions.

Turning to the proteins the same holds good in general. We have, first, the formation of simple amino-compounds which have not yet been isolated and proved to take part in the synthesis. From these, by dehydration, the proteins are formed. After this, by fermentation, we get simpler substances produced which are classed as albumoses. Further degradation yields peptones, which are closely akin to the albumoses: and finally the material breaks down into polypeptides and simple amino-acids.

3. *Possible Reactions in Vital Syntheses.*

In attempting to deduce the actual processes which lead to the formation of natural products, we are faced by two facts. In the first place, we are able to rule out as impossible such reactions as depend upon high temperatures and violent reagents; but, in the second place, we are not entitled to assume that, because up to the present we have not succeeded in making a reaction "go" at ordinary temperatures, it is therefore impossible for such a reaction to proceed effectively under these conditions. The safest course is obviously to confine ourselves as far as possible to reactions involving mild reagents and capable of proceeding economically at ordinary temperatures; though at the same time we need not exclude other reactions entirely.

Limiting ourselves thus, the choice before us is by no means so restricted as might at first be expected. Polymerization, condensation, hydrolysis, hydration and other addition reactions, dehydration, oxidation, reduction, and intramolecular change are all reactions which are known to be capable of taking place at ordinary temperatures.

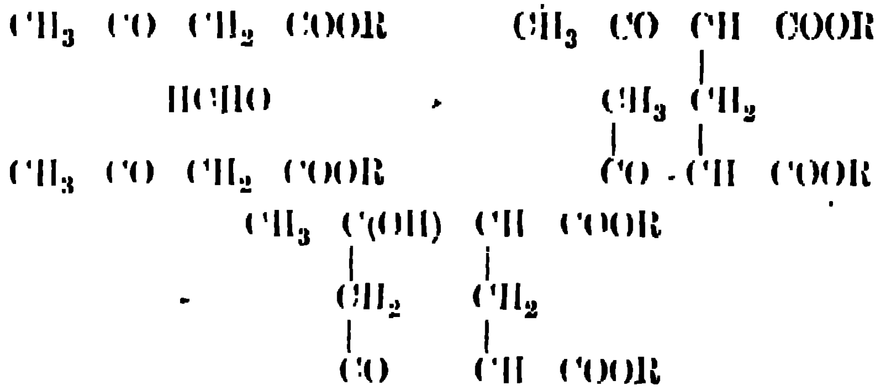
With regard to polymerization the data are too numerous to need reference in detail. The polymerization of aldehydes, the production of truxillic acid from cinnamic acid under the action of light, the conversion of ethylene into higher hydrocarbons, and the synthesis of rubber from isoprene are too well known to render it necessary to discuss them.

When we come to condensation the matter demands a more careful scrutiny; for various types of reaction are involved, each of which has its particular application to the problem before us.[1]

The aldol condensation[2] can be carried out with the help of traces of foreign materials; and it is noteworthy that among these catalysts are to be found salts such as the acetates, carbonates, and bicarbonates of the alkalis, all of which might be found in the saps of plants.* Now the aldol condensation not only provides a means whereby carbon chains may be formed from shorter groups—

$$CH_3.CHO + CH_3.CHO = CH_3\text{-}CH(OH)\text{-}CH_2\text{-}CHO$$

but in addition it also gives rise to carbocyclic derivatives[3]—



The benzoin condensation might also be reckoned as a probable vital reaction, for, although it is usual to employ heat in the laboratory, it seems evident that this condensation proceeds at ordinary temperatures at a slower rate.

The second class of condensation under consideration includes those reactions in which ammonia molecules or their substitution products take part. Of these, apart from amide formation, the most important is the production of amino-alcohols from aldehydes:—

$$R.CH:O + NH_3 = R.CH(OH)\text{--}NH_2$$

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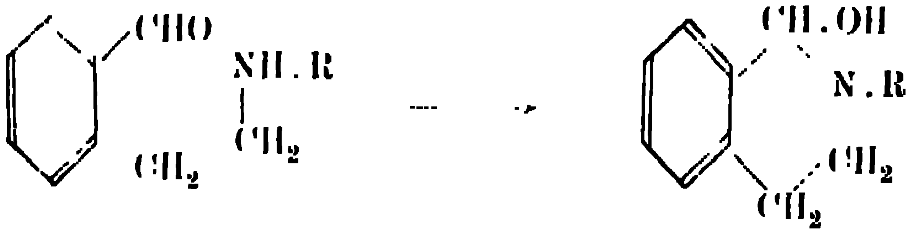
[1] See Baeyer, *Ber.*, 1870, **3**, 63.

[2] See Robinson's suggestions on this point (*Trans.*, 1917, **111**, 876); compare Rapor, *Trans.*, 1907, **91**, 1881.

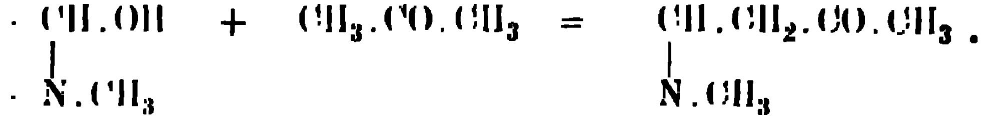
* The actual catalyst may be the hydroxyl ion.

[3] Rabe, *Annalen*, 1908, **360**, 265.

An intramolecular application of this reaction, in which an amino-aldehyde is employed, leads to ring-formation and the production of an amino-alcohol of the following type:—

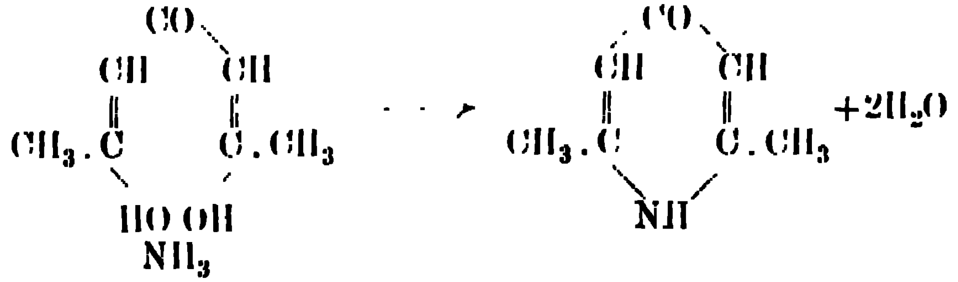


And, as Robinson[1] has shown, these amino-alcohols react readily in aqueous solutions with ketones, producing new derivatives by the elimination of water:—



$$\begin{array}{l}\cdot\,\mathrm{CH.OH}\\ \;|\\ \cdot\,\mathrm{N.CH_3}\end{array} + \mathrm{CH_3.CO.CH_3} = \begin{array}{l}\mathrm{CH.CH_2.CO.CH_3}\\ |\\ \mathrm{N.CH_3}\end{array}.$$

Different in nature is the ring-formation produced when such substances as diacetylacetone are treated with ammonia.[2] Here one molecule of ammonia interacts simultaneously with two hydroxyl radicles—the ketone enolizing—in order to produce a derivative of pyridine:-



Turning to the question of hydrolysis, it is unnecessary to dwell at length upon the ordinary reactions. Attention must be drawn, however, to the fact that the same reagents may produce different end-products according to the conditions employed. Thus acetoacetic ester derivatives may yield either a ketone or an acid in addition to acetic acid, in the ordinary acetoacetic ester synthesis.

The most important reagents in this field, however, are the enzymes; and it may be worth while to deal with their action in more detail. For the hydrolysis of the proteins, two classes of enzyme are known, which are termed proteolytic. The pepsin group attack albumins only in weak acid solutions; converting them into albumoses and peptones, which are soluble albuminous compounds of complicated structure. The trypsin group, on the other hand, acts only in neutral or weakly alkaline solution. A third class of enzymes, the labenzymes, have the faculty of coagulating protein compounds and are therefore termed coagulating enzymes. To some extent a fourth type of enzyme might be included in this section, since its reaction resembles those of the proteolytic class in so far that it depends upon the hydrolysis of the amide group. This last type has the faculty of breaking down urea and uric acid derivatives. The lipolytic enzymes are utilized to break down fats, from which they liberate glycerine. They appear to react best in acid solution.

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[1] Robinson, *Trans.*, 1917, 111, 876.

[2] Collie, *Trans.*, 1907, 91, 1806.

Several enzymes are known which can be employed to hydrolyse such materials as starch; and the progress of the hydrolysis depends upon the enzyme chosen. Thus when diastase acts upon starch it converts it into soluble material and breaks it down eventually to simple carbohydrates, the end-product being maltose, $C_{12}H_{22}O_{11}$. The application of maltase carries the process a stage further, two molecules of glucose being formed. Cane-sugar is broken down by invertase to glucose and fructose.

In all these cases, of course, the enzyme acts merely as a catalytic agent and has no influence upon the equilibrium point. Thus, as has been mentioned in a previous chapter, chlorophyllase may be employed either to hydrolyse a phytyl ester or to replace the phytyl radicle by an ethyl group.

Under the head of addition reactions it is only necessary to mention one or two processes. Among the unsaturated compounds, and especially in the terpene group, water can be added on to double bonds at ordinary temperatures when acids are present.[1] Apparently the reaction takes place in two stages: a molecule of acid first attaching itself to the double linkage in order to form an ester which is then hydrolysed, leaving an alcohol.

Under ordinary conditions also, ammonia has the faculty of attacking certain ethylenic linkages. Thus mesityl oxide takes up a molecule of ammonia to form diacetonamine—

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[1] Wallach, *Annalen*, 1908, 360, 102.

$$(CH_3)_2C:CH.CO.CH_3+NH_3=(CH_3)_2C(NH_2).CH_2.CO.CH_3$$

Dehydration is a reaction capable of almost endless applications in the field of vital chemistry. Saturated compounds may be converted into unsaturated derivatives; carbon chains may be formed, as in the mesityl oxide and phorone syntheses; benzene derivatives and heterocyclic substances such as pyrones can be prepared without exceeding ordinary temperatures. Indeed, it seems probable, though not yet proved, that a large proportion of vital syntheses depend upon successive dehydrations and rehydrations, by means of which the structure of the molecule can be altered.

As to oxidation and reduction, no doubt can be entertained as to the prominent part taken by them in vital reactions. As far as oxidation goes, we are acquainted with numerous enzymes (oxidases) which act as agents in the reactions of living tissue; and though the nature of the corresponding reducing enzymes, the reductases, has not been fully studied, there seems to be no question about their existence. Apart from enzyme action, numerous cases of spontaneous oxidation are known to the organic chemist, such as the formation of indigo from indoxyl and the production of oxyhaemoglobin from haemoglobin.

Intramolecular change is a branch of the subject which it is hardly necessary to treat in detail; but the pinacone change, the Beckmann rearrangement, and the benzilic acid change may be mentioned, since they may serve to throw light upon vital reactions. The most important of all is the keto-enol rearrangement; but this will be fully described in a later section.

In a previous chapter we have already encountered some examples of an intramolecular rearrangement which is of the greatest importance from the point of view of natural terpene syntheses: the formation of cyclic compounds from open-chain di-olefinic derivatives. The cases of citronellal and isopulegol (p. 88); rhodinal and menthone (p. 94); citral and cyclo-citral (p. 96); and the conversion of geraniol, nerol, and linalool into terpineol (p. 101), are examples of the type to which we refer. These changes take place either spontaneously or under the influence of alkali or acid; and it seems not improbable that some such rearrangement leads to the production of terpenes in nature.

Among natural products, methylamine derivatives occur; and it appears probable that these are formed by the action of formaldehyde:—

$$2NH_3 + 3CH_2O = 2NH_2.CH_3 + CO_2 + H_2O$$

In laboratory practice the reaction takes place even at the temperature of a water-bath; so that it evidently can be carried out, though slowly, under ordinary conditions.

Photochemical effects must, of course, play a very striking part in vital processes, especially in the vegetable kingdom. Of these, the most important from the theoretical standpoint is the discovery by Cotton[1] that the dextro and lævo forms of tartaric acid absorb *d*-circularly polarized light to different extents; which implies that such light will decompose them at different rates. Now since light is circularly polarized by the surface of the sea, we have a natural method whereby the production of unequal quantities of asymmetric material can be attained; and once the balance between the two isomers is thus disturbed, the general production of optically active compounds becomes possible. It may be that these experiments indicate the manner in which optically active substances first made their appearance on the earth's surface.

4. *The Production of Carbohydrates.*

In searching for the reservoirs from which plants draw their supplies of carbon wherewith to build up their tissues, we are limited by the fact that plant nourishment can take place through only two channels, the roots and the leaves. As far as the supply of carbon is concerned, it may at once be granted that the roots play no preponderant part. Plants can be forced to grow under conditions which preclude the possibility of any great supply of carbon through the root; and yet the organism seems to suffer nothing by this source of material being cut off. We are, therefore, thrown back upon the leaves as the essential agents in carbon assimilation.

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[1] Cotton, *Ann. Chim. Phys.*, 1896, VII., 8, 373.

The source from which leaves can obtain carbon compounds is obvious: the carbon dioxide of the air suffices to furnish all the carbon which the plant requires for its growth; and it only remains to consider how this is utilized by the organism.

Strangely enough, the next stage in the process is one which has given rise to most controversy.[1] It seems not improbable that the reaction takes the following form: —

$$H_2CO_3 + 2H_2O \rightleftharpoons H.CHO + 2H_2O_2$$

If, now, an enzyme be present which has the power of decomposing hydrogen peroxide,[2] there will be a continual progress from left to right of the equation, with a steady accumulation of formaldehyde in the leaf.[3] The energy required to effect this reaction must originally be drawn from solar radiation; but the immediate cause of the transformation may be due to electrical conditions on the leaf surface.[4]

Assuming that formaldehyde is thus formed, clearly it does not remain unaltered; for it was only with considerable difficulty that the presence of this substance in plant leaves was determined.[5] Evidently we are led to assume, further, that the formaldehyde is changed almost immediately into some other substance; and the experiments of Loew,[6] Fischer and Passmore[7] have shown that in presence of calcium hydrate a dilute solution of formaldehyde can be polymerized direct to racemic fructose. It seems very doubtful, however, if this simple process represents what occurs in the plant; for the sugars obtained by phytological methods are optically active, so that an asymmetric agent must make its appearance at some stage or other during their synthesis. Two alternative solutions of this problem may be considered. In the first place the agent which stimulates the polymerization of the sugar may be itself asymmetrical (an enzyme); and thus one enantiomorph may be formed in greater quantity than the other: or possibly the racemic sugar is produced by direct methods and is then acted upon by a selective enzyme such as are common in plants, with the result that one antipode is more rapidly decomposed than the other. In either way a preponderance of one active form would result. It must be frankly admitted that even in this simple problem we can only say that we do not know the true solution.

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[1] See Jörgensen and Stiles, *Carbon Assimilation*; Meldola, Presidential Address, *Trans.*, 1906, **89**, 745, and also Haas and Hill, *The Chemistry of Plant Products*, p. 151 ff.

[2] Loew, *Ber.*, 1902, **35**, 2487.

[3] See Gibson, *Ann. of Botany*, 1908, **22**, 117.

[4] *Ibid.*

[5] *Ibid.*

[6] Loew, *J. pr. chem.*, 1886, **33**, 321.

[7] Fischer and Passmore, *Ber.*, 1889, **22**, 359.

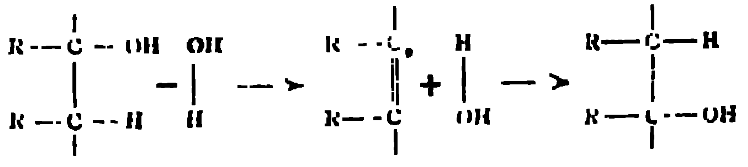
With the production of sugars of the hexose type, however, the main difficulties are ended, for by the action of enzymes these can be converted into much more complex materials, the polysaccharides;[1] and even higher complexes such as dextrin can be produced from the hexoses by catalytic means. As to the further stages by which cellulose and its analogues are formed, we can only admit our ignorance; though the fact that these substances can be reduced to simpler materials by catalytic action certainly suggests that they are probably built up by a similar process.

5. *Collie's Theory of Enzyme Action.*

† During the break-down of certain carbohydrate derivatives under the action of enzymes, an important step in the reaction is evidently the accumulation of hydrogen atoms at one end of the chain and the gathering of oxygen atoms at another point. Only on this assumption can we explain the conversion of the radicle (I.) into the grouping (II.) which evidently takes place during alcoholic fermentation:—

$CH_2OH—CH.OH—$ (I.) $CH_3—CH_2—$ (II.)

Now if the sugar molecule be regarded as being built up from a chain of carbon atoms united with water molecules, such a transformation can readily be represented by a mere change in orientation of the hydrogen and hydroxyl radicles, which might be produced by dehydration and rehydration:—



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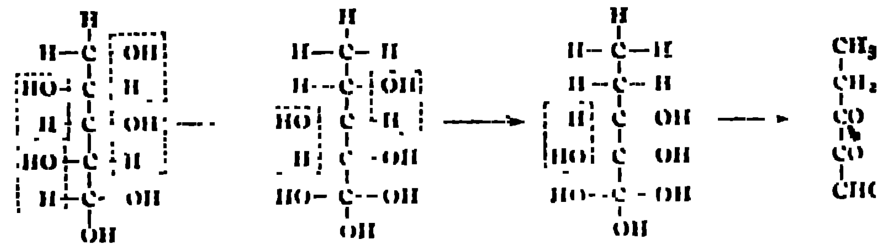
[1] Hill, *Trans.*, 1898, 73, 634; see also Bayliss, *The Nature of Enzyme Action.*

† In the case of a pentose, distinguishing the inverting groups by the dotted lines, we should get the following picture:—



† Take the case of a hexose as an illustration of the next step in the argument. At one end of the chain is the weakly basic hydroxyl group, whilst at the other end lies the aldehyde radicle, which, in its ortho-form, is weakly acidic. It is therefore reasonable to assume that the main chain of the sugar is subjected to electrical strain. Now if this electrical condition can be interfered with, changes might be expected to occur in the molecule; and it is possible that the enzymes work in this manner. The enzyme molecule is probably built up from amino-acids somewhat in the same manner as a protein; so that it contains, like the sugar, a basic group ($-NH_2$) and an acidic radicle ($-COOH$). From what we know of their molecular complexity, the enzyme molecules must be immensely greater than the molecules of simple carbohydrates; and it is therefore probable that one molecule of enzyme may react simultaneously with hundreds of carbohydrate molecules. The basic and acidic groups of the sugar will come into contact with the acidic and basic portions of the enzyme *provided that these groups occupy suitable positions in space*; ¹ the system is then short-circuited; and what might be termed "molecular electrolysis" results; the energy of the sugar molecule is set free as heat; and, by the rearrangement of the hydrogen and hydroxyl groups of the sugar, new compounds are formed which are no longer capable of combining with the amphoteric enzyme. The latter may then be recharged by induction or by the presence of ions in the solution, as is the case with many colloids.

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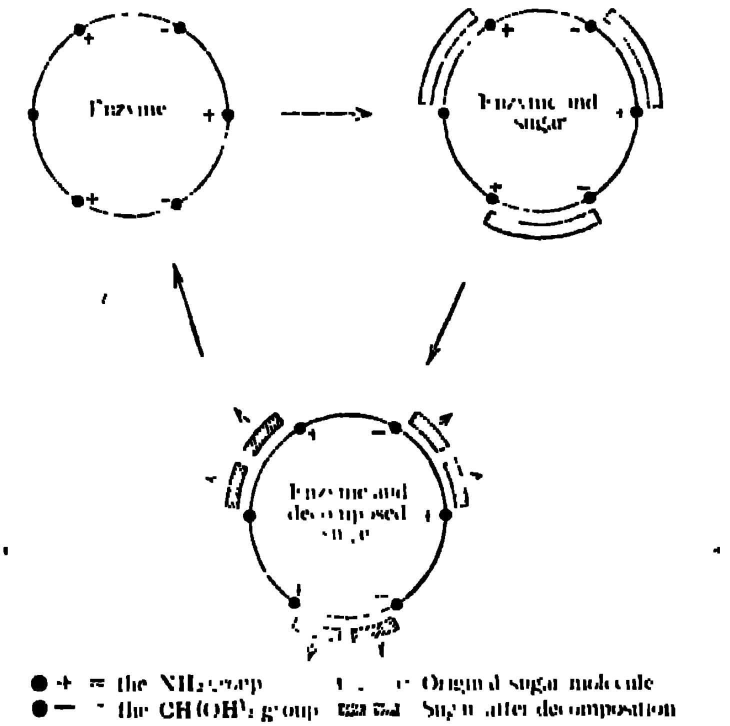
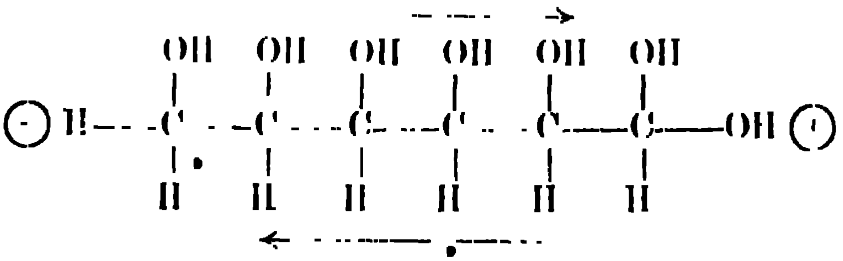
[1] This serves to explain the selective power of enzymes.

The following diagram represents the various steps in the process :—


Enzyme
Enzyme and sugar
Enzyme and decomposed sugar
+
−
● + = the NH₂ group
[illegible] = Original sugar molecule
● — = the CH(OH)₂ group
▨ = Sugar after decomposition

In its elements the Collie theory bears a strong resemblance to Ehrlich's side-chain theory of toxins and anti-toxins, the two groups at the points attacked being analogous to Ehrlich's receptors, whilst the corresponding points in the enzyme are akin to Ehrlich's haptophore groups.

† Another possibility must not be left out of account. When we examine the structural formula of a sugar in its ortho-form the similarity between it and one of the usual diagrams to illustrate electrolysis strikes the eye at once—



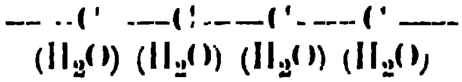
$$\begin{array}{ccccccccc} & & & & & \longrightarrow & & & \\ & & OH & OH & OH & OH & OH & OH & \\ & & | & | & | & | & | & | & \\ \ominus & H- & C- & C- & C- & C- & C- & C- & OH\ \oplus \\ & & | & | & | & | & | & | & \\ & & H & H & H & H & H & H & \\ & & & \longleftarrow & & & & & \end{array}$$

Now if we imagine a pair of terminals inserted in the molecule as shown by the + and — signs, it is clear that the hydrogen atoms would be drawn to the left, whilst the hydroxyl groups would move to the right. This would give us the same accumulation of hydrogen atoms at one end and hydroxyl groups at the other. Collie's conception of the action of enzymes allows us to picture the necessary electrical terminal inserted into the molecular structure of the sugar; and it may be noted that these terminals do not necessarily attack the two ends of the chain; they might quite as easily be supposed to be inserted at any point in the molecular structure which is spatially suitable for their entry; and in this way the selective action of different enzymes may be accounted for.

6. *A Dynamic Formula for the Sugars.*

One reaction which distinguishes the sugars from almost all other compounds is their dehydration. The ease with which they split off water leaving carbon behind, is one of their most marked characteristics; and it appear that less attention has been paid to the matter than might be profitable.

† On the basis of this reaction, a new way of regarding the sugar molecule has been proposed by Collie. Let us assume that the carbohydrate molecule is built up from a straight chain of carbon atoms combined with water molecules, thus:—



$$-\underset{(H_2O)}{C}-\underset{(H_2O)}{C}-\underset{(H_2O)}{C}-\underset{(H_2O)}{C}-$$

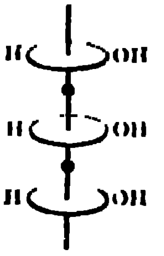
Assume, further, that these water molecules envelop the carbon atoms and *that the three atoms of the water molecule rotate round the carbon atom to which they are related.** If this rotation were entirely stopped, we should get the state of affairs represented by the usual graphic formulæ for the sugars, each hydrogen and hydroxyl group taking up its favoured position with regard to the rest of the chain. The rotation of the water molecules might, of course, be either right or left-handed.

† Now since atoms are electrical systems, this spinning of the water molecules about the carbon atoms would have the same effect as placing the carbon chain in a magnetic field; and hence on this assumption it is possible to explain the optical rotatory power of the sugars.

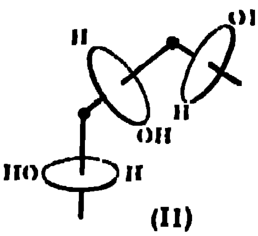
---

* If the reader will clear his mind of the antiquated conception of directed valency he will have no difficulty in seeing that this idea in no way contravenes any fundamental chemical postulate.

† The energy put into the system by sunlight would be converted into *the increased rotational energy* of the water atoms round the carbon atoms. The action of enzymes might be supposed to be a braking effect which would tend to slow up the rotational energy and reduce the molecule to a condition represented by the ordinary static formula. When the water molecules are at their highest rotational velocity, the system would tend to bring the axes of rotation parallel, as in (I.); but when the braking effect came in there would be more tendency to librate and the system would approach the position (II.):—



(I)



(II)

Under such conditions the hydrogen and hydroxyl groups would, at certain points in their orbits, come more or less close together, when either water could be eliminated from the system or the hydrogen of one carbon might exchange places with the hydroxyl group of the next carbon atom—

$$\text{CH.OH}\;\;\text{CH.OH}\cdot \begin{cases} \rightarrow \;\; \text{CH}{=}\text{C(OH)} - \\ \rightarrow \cdot\;\text{CH}_2\;\;\text{C(OH)}_2\;\cdot \end{cases}$$

† As can be seen by working out the problem, it is possible to pass from a right-handed spin through the symmetrical keto-methylene grouping to a final phase in which a left-handed spin exists; so that the theory covers the case of racemization satisfactorily and also such cases as the production of lævorotatory lævulose from dextrorotatory glucose via the osazone.

7. *The Polyketides.*

As will be seen in later sections of this chapter, substances containing the keto-methylene grouping, $—CH_2.CO—$, or its tautomeric form, $=CH.C(OH)-$, play a large part in some natural processes; and it is therefore desirable to have some general term to cover the class of compounds which contain linked keto-methylene chains. Collie[1] proposes to name *polyketides*[2] those compounds which may be regarded as built up by the polymerization of keten and the subsequent addition of a molecule of water—

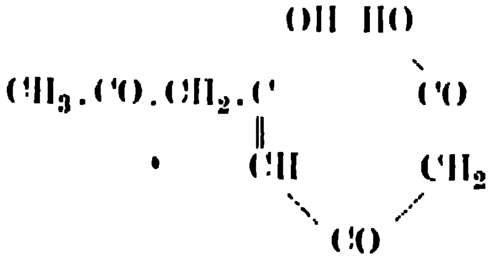
$H.(CH_2CO).OH$	$H.(CH_2CO)_2.OH$	$H.(CH_2CO)_3.OH$
A monoketide (Acetic acid).	A diketide (Acetoacetic acid).	A triketide (Triacetic acid).

The members of the polyketide series are marked by two characteristics: their extreme sensitiveness to slight variations in the concentration of the reagents used upon them; and the readiness with which they undergo intramolecular change. It is unnecessary to multiply examples of their behaviour, but several typical ones must be given to show the ease with which polyketides or their derivatives can be converted into members of aliphatic, aromatic, and heterocyclic groups:—

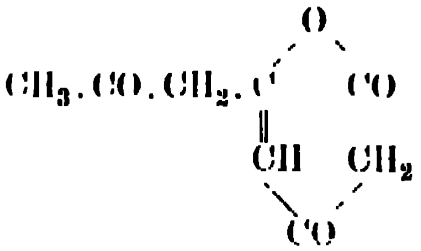
Let us take as our starting-point tetracetic acid: –

$$CH_3.CO.CH_2.CO.CH_2.CO.CH_2.COOH$$

This substance does not exist in the free state, but loses water at once, giving a ring compound, dehydracetic acid:



Tetracetic acid (Enolic form).



Dehydracetic acid (Tetracetic lactone).

Dehydracetic acid, when heated with mineral acids, gives rise to salts of dimethyl-pyrone. The first stage in the reaction is the formation of tetracetic acid, which then loses a molecule of carbon dioxide from its carboxyl radicle; diacetyl-acetone is thus produced, which enolizes in a new position; finally, water is eliminated and dimethyl-pyrone remains:—

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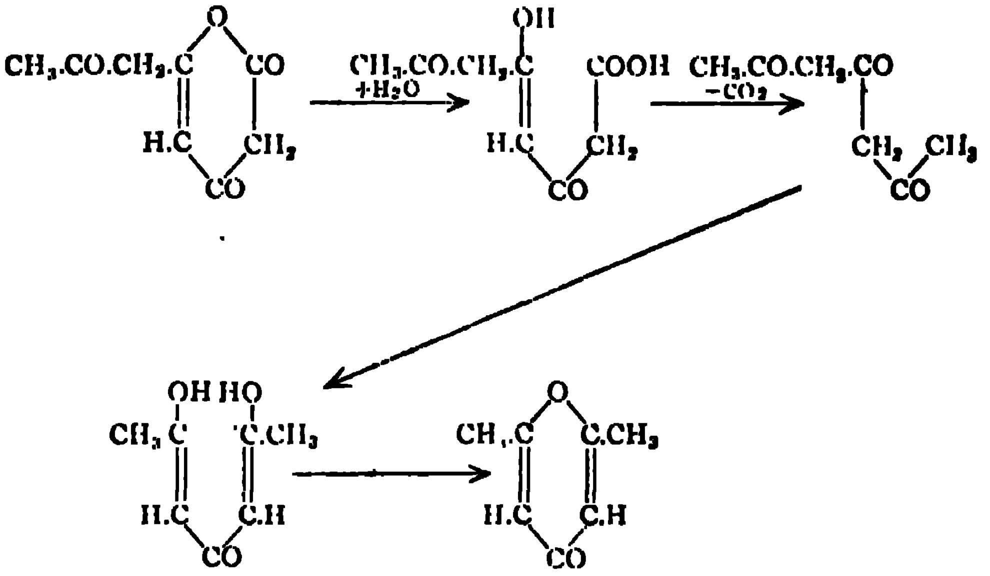
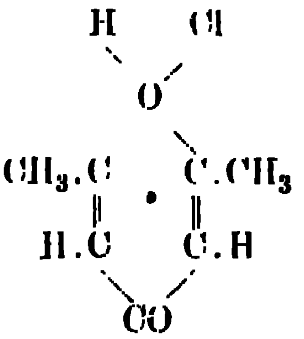
[1] Collie, *Proc.*, 1907, 23, 230.

[2] For a general account of polyketide reactions, see Collie, *Trans.*, 1907, 91, 1806.



When the dimethyl-pyrone thus obtained is analysed, however, it is found to have the composition $C_7H_9O_2Cl$, which corresponds to a compound of one molecule of dimethyl-pyrone with one molecule of hydrochloric acid. The substance is not a chlorine-substituted pyrone derivative, but behaves exactly like the hydrochloride of an organic base. Collie and Tickle,[1] who were the discoverers of this class of substance, prepared a series of compounds of dimethyl-pyrone with many of the common acids, both organic and inorganic, as well as metallic double salts; and from a study of their properties drew the conclusion that the oxygen atom which forms the bridge in the pyrone nucleus has basic properties akin to those of a tertiary nitrogen atom. Thus, just as tertiary amines form ammonium salts, divalent oxygen compounds may unite with acids to form "*oxonium salts.*" The compound of dimethyl-pyrone with hydrochloric acid would on this hypothesis be represented by the formula—



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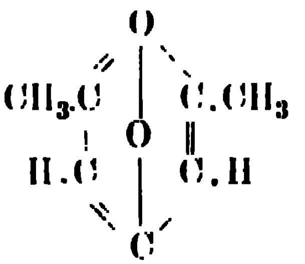
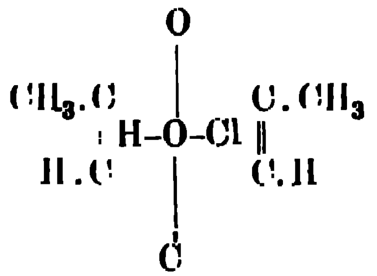
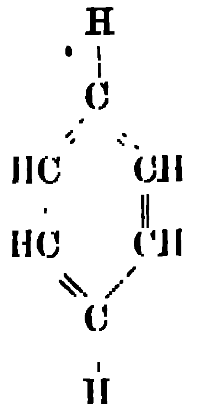
[1] Collie and Tickle, *Trans. Chem. Soc.*, 1899, **75**, 710.

Though dimethyl-pyrone contains a carbonyl group, it does not react with either hydroxylamine or phenylhydrazine. This peculiar behaviour has led Collie[1] to put forward the view that not one but both the oxygen atoms in the pyrone nucleus are quadrivalent in the oxonium salts; while in the base itself one oxygen atom is supposed to be always quadrivalent. On this view the formulæ of dimethyl-pyrone and its hydrochloride would be written thus—

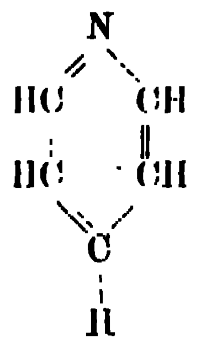




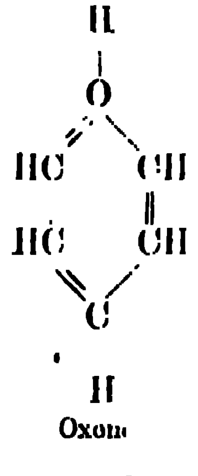
This view of the pyrone structure is supported to a certain extent by an examination of the refractive indices of pyrone derivatives which has been carried out by Miss Homfray.[2] In both of the above formulæ the peculiar resemblance to the benzenoid type is manifest, and Collie has been led to suggest that the root-substance of the pyrone class has a structure which resembles that of pyridine. To this hypothetical compound* he has given the name "*oxene*,"[3] as it is the oxygen analogue of benzene and pyridine—



Benzene.



Pyridine.



Oxene

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[1] Collie, *Trans. Chem. Soc.*, 1904, 85, 971; *cf.* Willstätter and Pummerer, *Ber.*, 1904, 3733; 1905, 38, 1461.

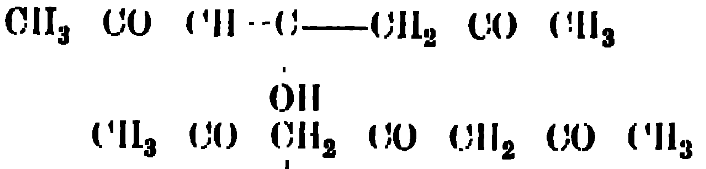
[2] Homfray, *Trans. Chem. Soc.*, 1905, 87, 1443.

* This type of heterocyclic ring is actually found in the pyrylium series.

[3] Collie, *Trans. Chem. Soc.*, 1904, 85, 971*f*.

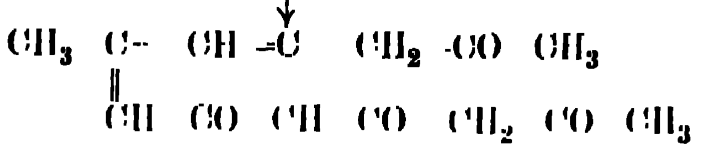
Dimethyl-pyrone, under the action of alkali, yields salts of an enolic form of diacetyl-acetone, from which diacetyl-acetone itself can be obtained by adding acid.

This tetraketide derivative, diacetyl-acetone, shows a most extraordinary series of changes. On standing in a desiccator, it loses water and is reconverted into dimethyl-pyrone; with ammonia it yields a pyridine derivative, lutidone; in very weak alkaline solutions at ordinary temperatures it produces a benzene derivative which, in presence of very slightly stronger alkali, changes to a naphthalene compound:—

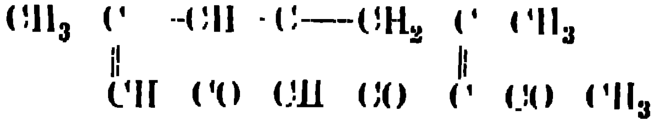


$CH_3\,CO\,CH{=}\underset{OH}{C}{-}CH_2\,CO\,CH_3$

$CH_3\,CO\,CH_2\,CO\,CH_2\,CO\,CH_3$ Diacetyl-acetone.

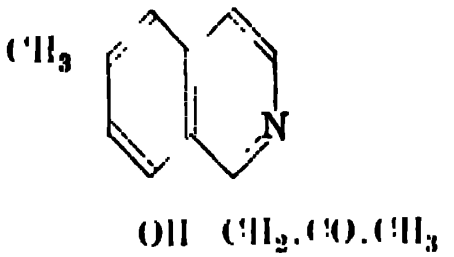


Benzene derivative (Ketonic form).



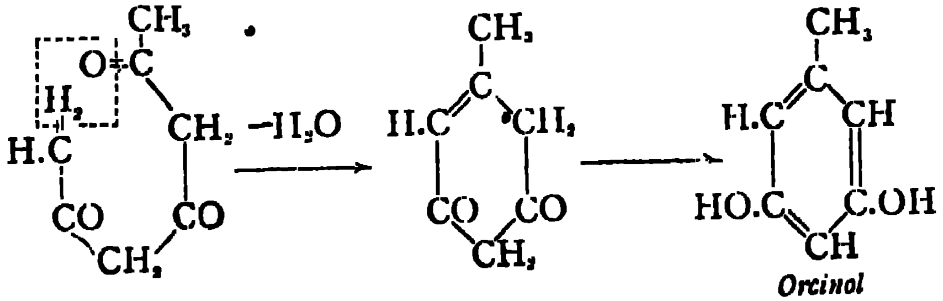
Naphthalene derivative (Diketonic form)

By the action of ammonia on the benzene derivative, an iso quinoline compound—



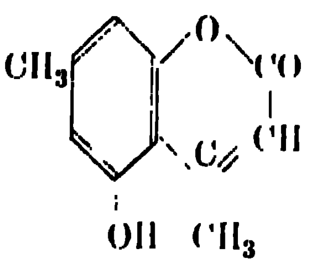
is formed.

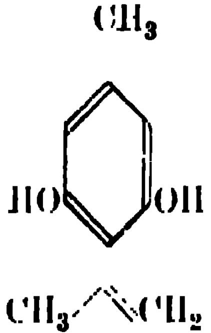
Returning to the dehydration of diacetyl-acetone, the use of acid reagents produces another benzene derivative, orcinol—



Orcinol

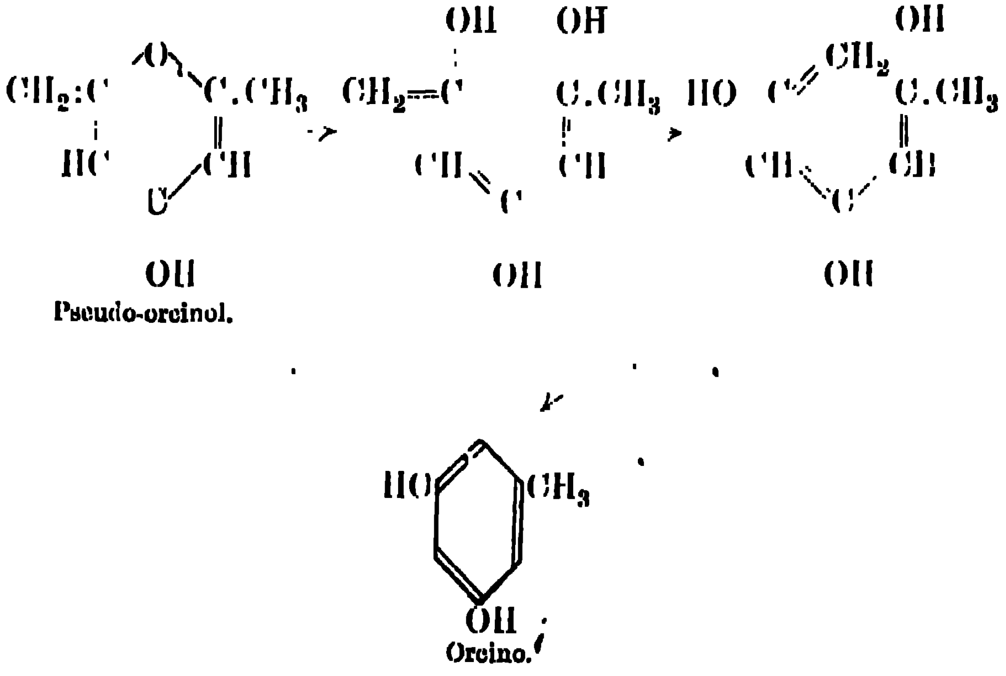
Further results are obtained by condensing the polyketide orcinol with acetoacetic ester. The reaction product, after hydrolysis, is found to be dimethyl-umbelliferone (I.)—


(I.)


(II.)

and when this compound is treated with alkali and heated, it undergoes hydration and loss of carbon dioxide with the formation of a thymol derivative (II.). Orcinol also condenses with the polyketide derivative acetylacetone, yielding a benzpyrone compound, the formula of which is given on p. 258.

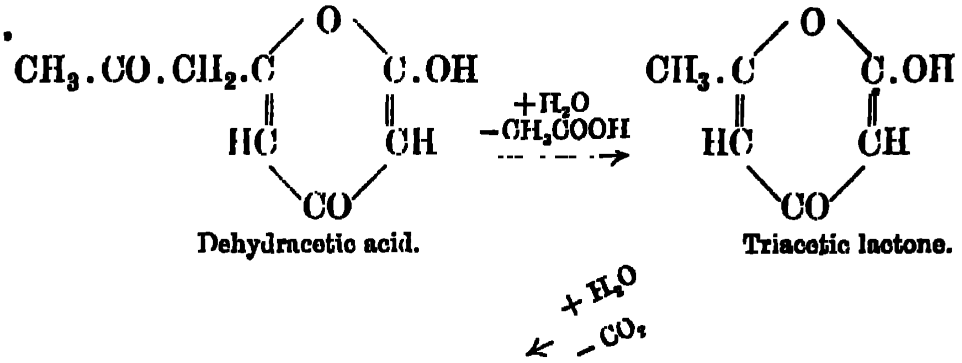
An interesting compound, pseudo-orcinol, bridging the gap between the pyrone and benzene series, was discovered by Collie and Stewart. As can be seen from its formula, the wandering of a hydrogen atom will convert it into dimethyl pyrone; whilst hydration, followed by rearrangement and dehydration, yields orcinol. In practice, acid solutions convert it into dimethyl-pyrone, whilst alkali changes it to orcinol—


Pseudo-orcinol.

Orcino.

Collie[1] has obtained the diacetyl derivative of this substance by another method. When treated with acids it yields diacetyl-dimethyl-pyrone; whilst alkali converts it into diacetyl-orcinol.

The foregoing reactions, of which a tabular scheme is given on p. 258, are sufficient to show the manifold possibilities of the polyketide group. To complete the survey it is necessary to mention the ease with which the polyketides are hydrolysed to simpler derivatives. Dehydracetic acid is decomposed by either acids or alkalis; and, if the hydrolysis be conducted under conditions which allow the intermediate products to be isolated, the following stages are observed :—



Dehydracetic acid.

Triacetic lactone.

$$CH_3.CO.CH_2.CO.CH_3 \xrightarrow{+H_2O} CH_3.COOH + CH_3.CO.CH_3$$

Acetyl-acetone.

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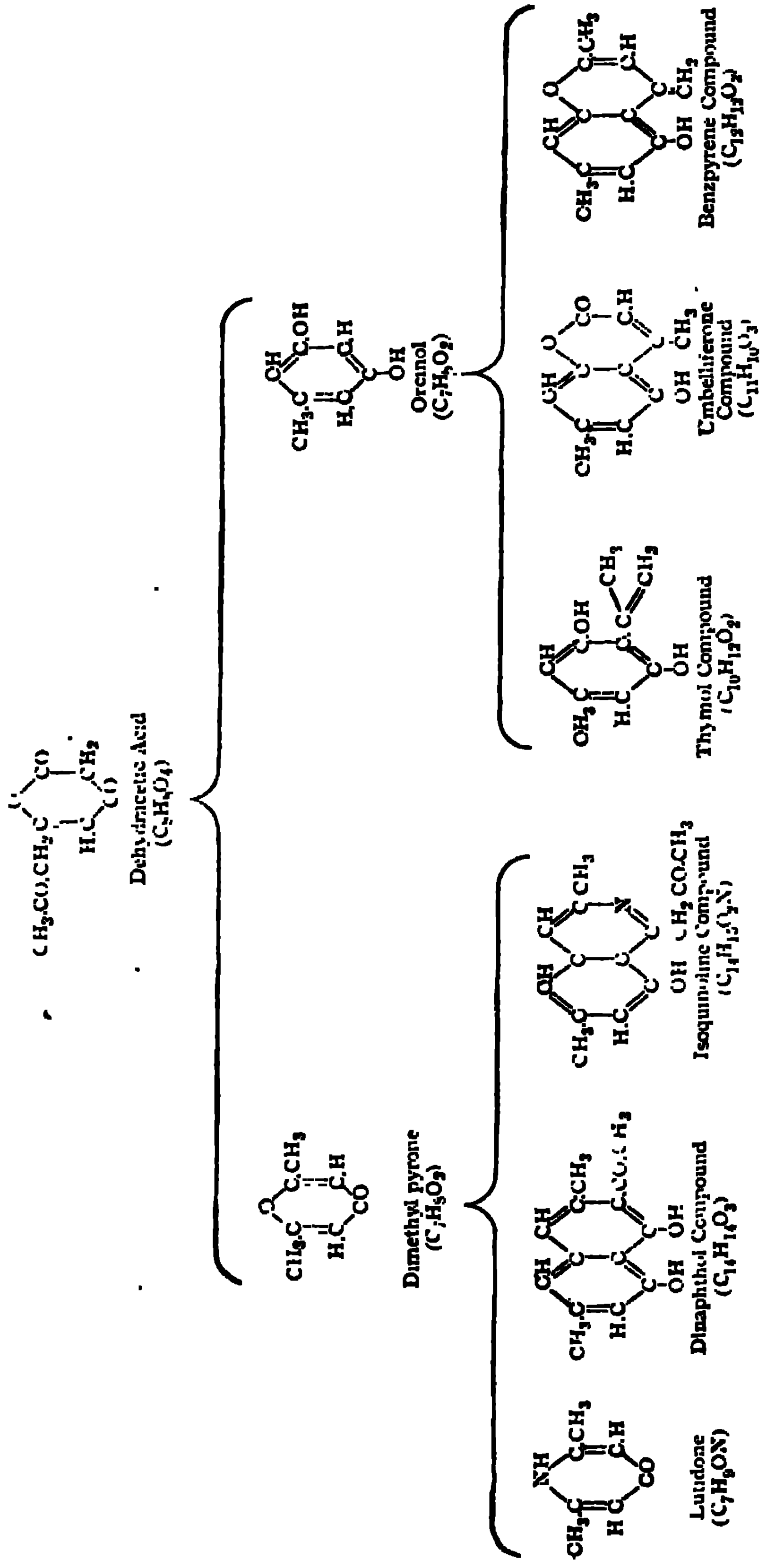
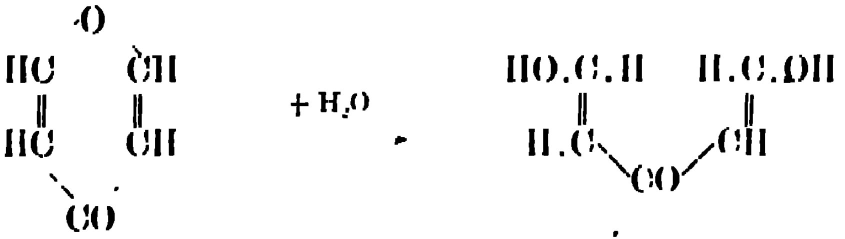
[1] Collie, *Trans.*, 1904, **85**, 971.


Dehydracetic Acid
($C_8H_8O_4$)
Dimethyl pyrone
($C_7H_8O_2$)
Orcinol
($C_7H_8O_2$)
Lutidone
(C_7H_9ON)
Dinaphthol Compound
($C_{14}H_{14}O_3$)
Isoquinoline Compound
($C_{14}H_{15}O_3N$)
Thymol Compound
($C_{10}H_{12}O_2$)
Umbelliferone Compound
($C_{11}H_{10}O_3$)
Benzpyrene Compound
($C_{13}H_{12}O_2$)

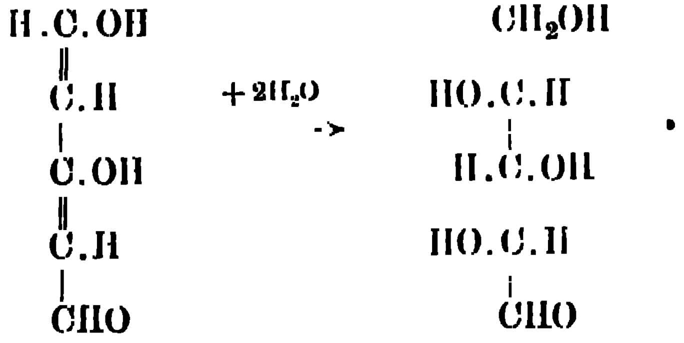
8. *The Relations between the Carbohydrates and the Polyketides.*

† Pyrone is acted upon by metallic alcoholates with the formation of derivatives of bishydroxy-methylene-acetone.[1] The proper conditions for carrying out a similar reaction with a water molecule instead of one of sodium ethylate have not yet been discovered; but the point is not without theoretical interest, as it suggests a means whereby sugars may be converted into polyketides and *vice versâ*. Taking the case of pyrone as an example, the following stages would be involved:—



Pyrone.

Bishydroxy-methylene-acetone.



A pentose.

A reverse series of reactions would lead from the carbohydrates to the polyketides and thence to all the classes of compounds which were enumerated in the last section.

Now, though it must be frankly confessed that up to the present our laboratory methods have failed to bring about either of these conversions,* there appear to be numerous data tending to show that many plant products are derived from polyketide chains; and since the carbohydrates form the most obvious source of polyketide derivatives it seems not unwarranted to assume that reactions similar to the above do take place in plants. If we do not make this assumption, we require so many different postulates in devising syntheses of vital products that the matter becomes extremely complicated; whereas by granting the possibility of polyketide production it may be rendered very simple.

---

[1] Willstätter and Pummerer, *Ber.*, 1905, 38, 1461.

9. *The Carbohydrates, Polyketides, and Benzene Derivatives.*

† The aromatic series is strongly represented among plant products; and it seems evident that the source of the vegetable benzene compounds must be sought in the carbohydrates and celluloses of the plant. The formulæ below indicate how benzene derivatives might be produced direct from the carbohydrates by means of simple dehydration followed by intramolecular rearrangement. Only two examples are given, as they are intended as illustrations and not as a complete list of possible changes. The groups involved in the dehydrations are printed in heavy type to make the matter clear.

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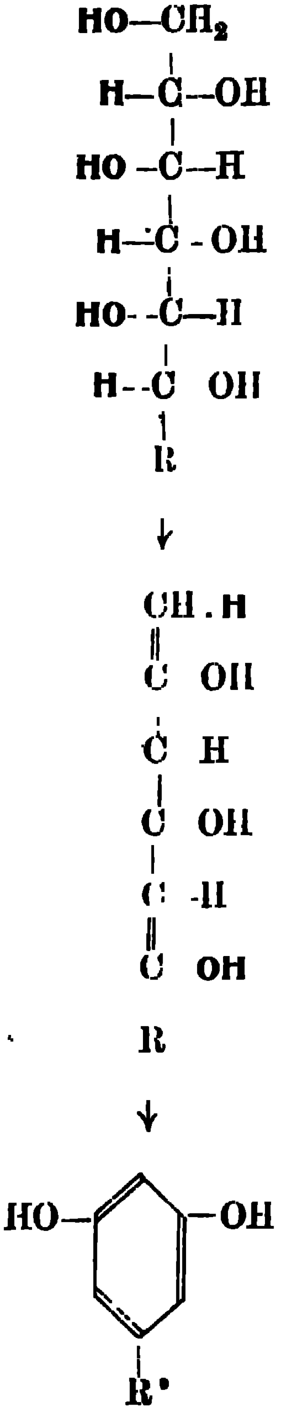
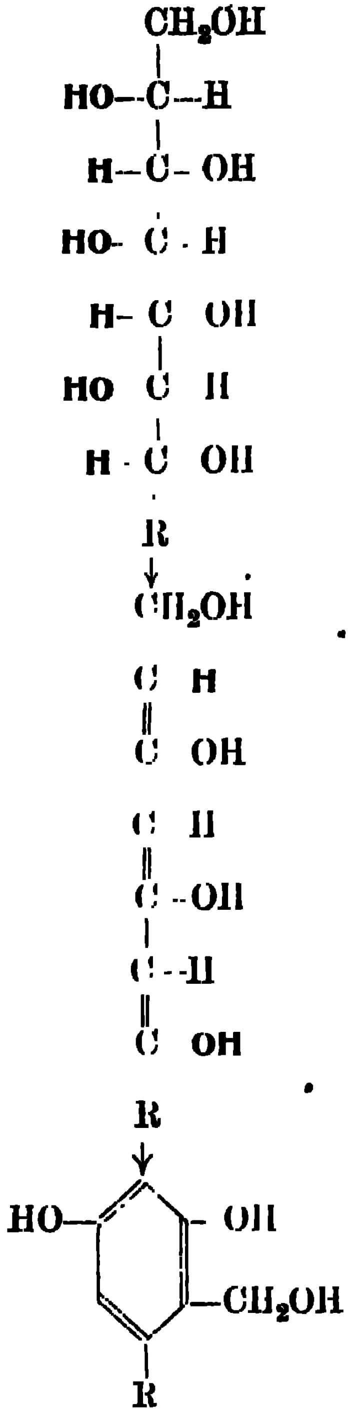
* One great difficulty in the way is the ease with which open-chain derivatives of the polyketide series are hydrolysed in presence of alkali or acid.

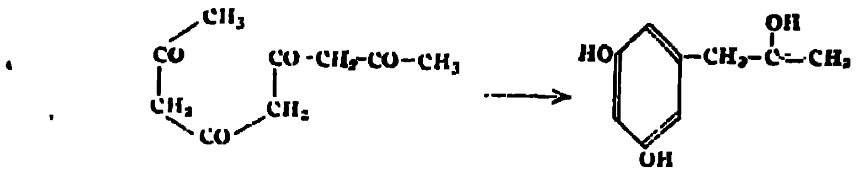


Orcinol derivative.



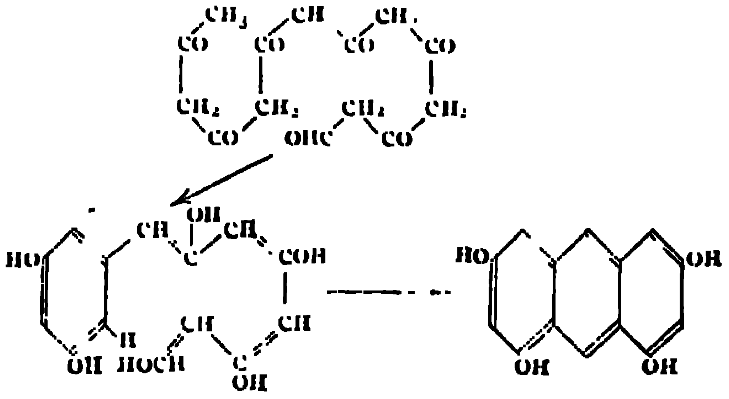
Ortho-derivative.

† If the production of polyketides from the carbohydrates be assumed in order to simplify the formulæ, the following scheme shows how unsaturated side-chains attached to benzene nuclei could be formed by dehydration and rearrangement :—



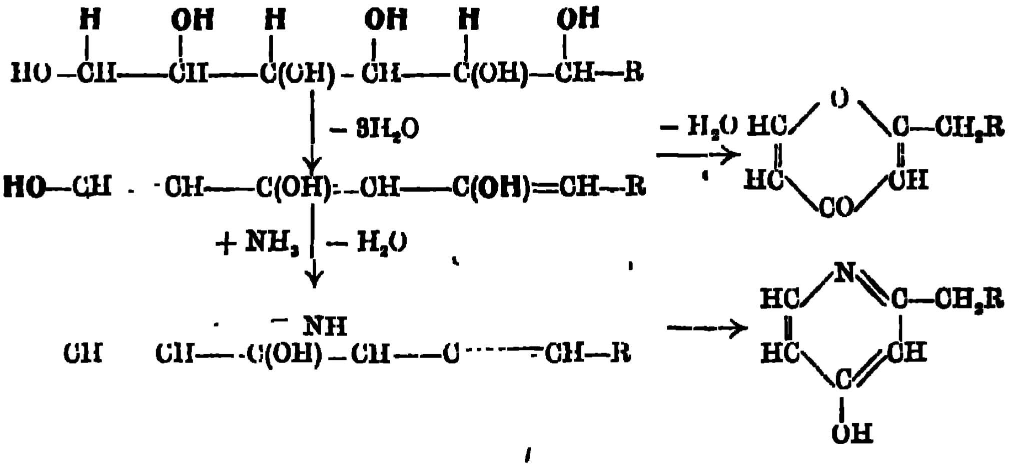
from which, by enzymatic reduction, an analogue of anethol would be formed.

† The production of anthracene derivatives could be accounted for in a similar manner:—



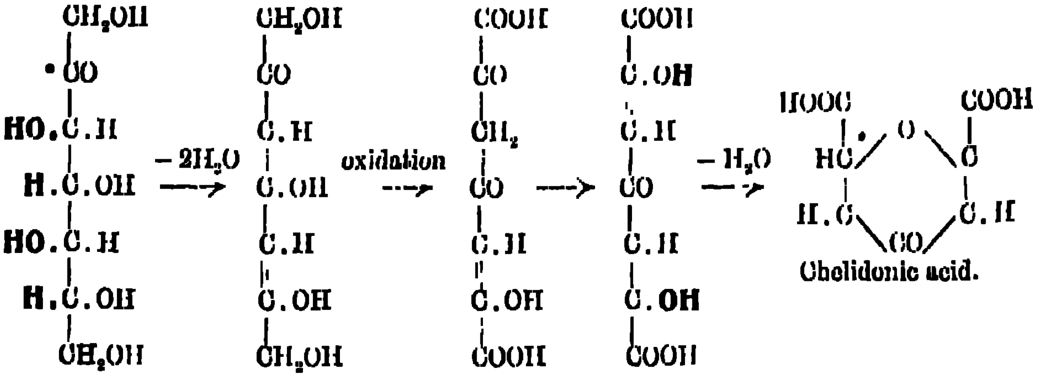
10. *The Formation of Pyrones and Pyridines from the Carbohydrates.*

The relations between the polyketides on the one hand and the pyrone and pyridine derivatives on the other have already been explained; so two examples will be sufficient to indicate the possibility of a direct passage from the carbohydrate series to the two heterocyclic groups. As before, the atoms involved in the dehydrations are printed in heavy type.



II. *The Genesis of Some Plant Pigments.*

The fact that many of the important plant colouring materials belong to the pyrone group suggests that they may be derived from polyketide chains and hence, indirectly, from the celluloses. In the simpler colouring matters the connection is almost obvious from an inspection of the formulæ; and one example will suffice. The case of chelidonic acid may be chosen, and its possible derivation from a heptose accounted for by the usual processes of dehydration and oxidation—

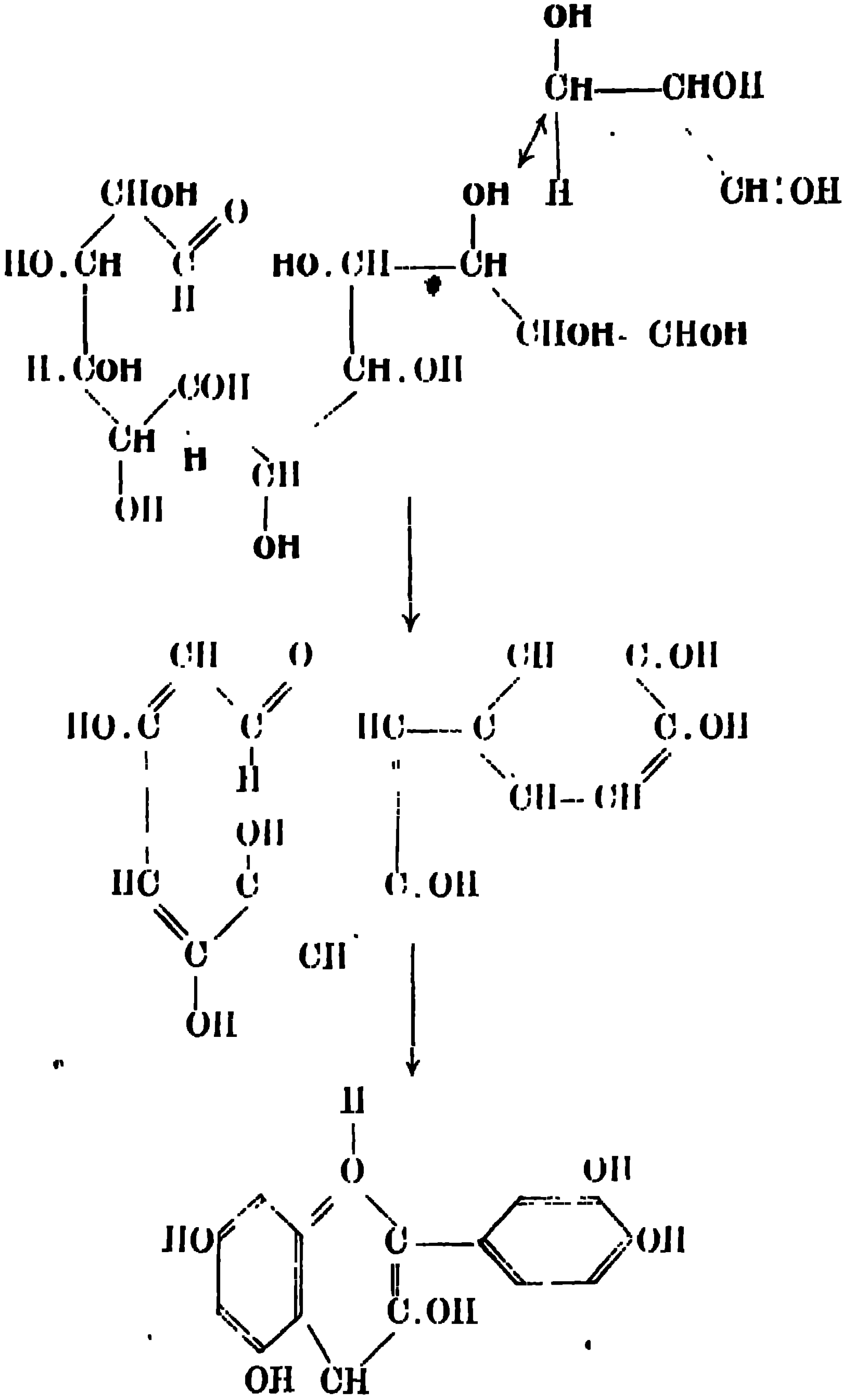


Chelidonic acid.

The benzo-pyrone group can be accounted for in a similar manner.

In the case of the anthocyanins, the reaction may be traced directly back to a carbohydrate chain without requiring the intermediate formation of a polyketide derivative at all. An examination of the formula of cyanidin, $C_{15}H_{12}O_6$, shows that it might be derived from a carbohydrate having the composition $C_{15}H_{30}O_{15}$ by the abstraction of nine molecules of water; and from cyanidin the corresponding anthocyanin is produced by the action of glucose. From the cyanidin, also, quercetin may be formed by oxidation; so that such a synthesis would open the way to the flavone series as well.

The following formulæ show how, by simple dehydration, it is possible to imagine the production of cyanidin from a carbohydrate of the structure $CH_2OH.(CH.OH)_{13}.CHO$. In order to make the steps clearer, the atoms eliminated by dehydration are printed in heavy type—



Cyanidin.

It is unnecessary to give further examples, as the reader can easily work them out for himself if he is interested in the point.

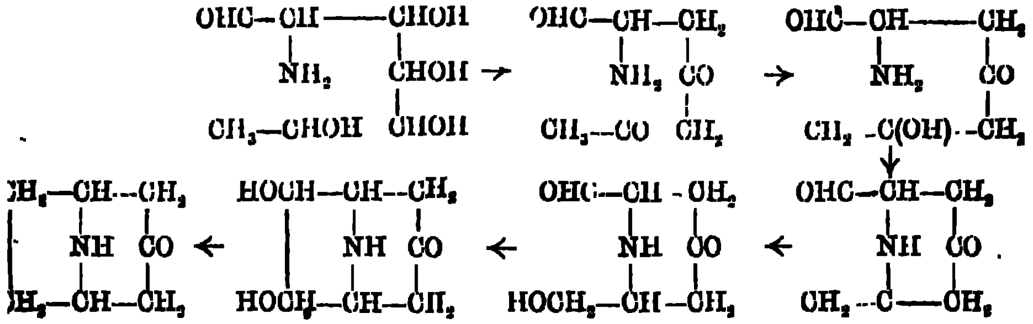
12. *The Alkaloidal Skeletons.*

With regard to the formation of the alkaloids, two views are possible. In the first place, the alkaloidal skeleton may be supposed to come into existence directly by the action of ammonia upon a long carbon chain derived from the celluloses; or, secondly, we may assume that the celluloses and proteins break down into smaller molecules which then take part in piece-meal syntheses of the larger alkaloid groupings. In either case, it will be seen that the production of alkaloids is to be regarded as a down-grade reaction.

The formation of tropinone furnishes a case to which both methods are applicable; so it may be given here as an example.

Let us assume that among the degradation products of cellulose a methyl-hexose-amine is produced. This will have the composition $C_7H_{15}O_5N$. Now nor-tropinone (i.e. tropinone without the methyl radicle attached to the nitrogen atom) has the composition $C_7H_{11}ON$. The difference between the two formulæ is H_4O_4; from which is is clear that dehydration alone will not suffice to pass from the one compound to the other; reduction to the extent of four hydrogen atoms is also necessary.

The steps in the conversion may be represented as follows:—

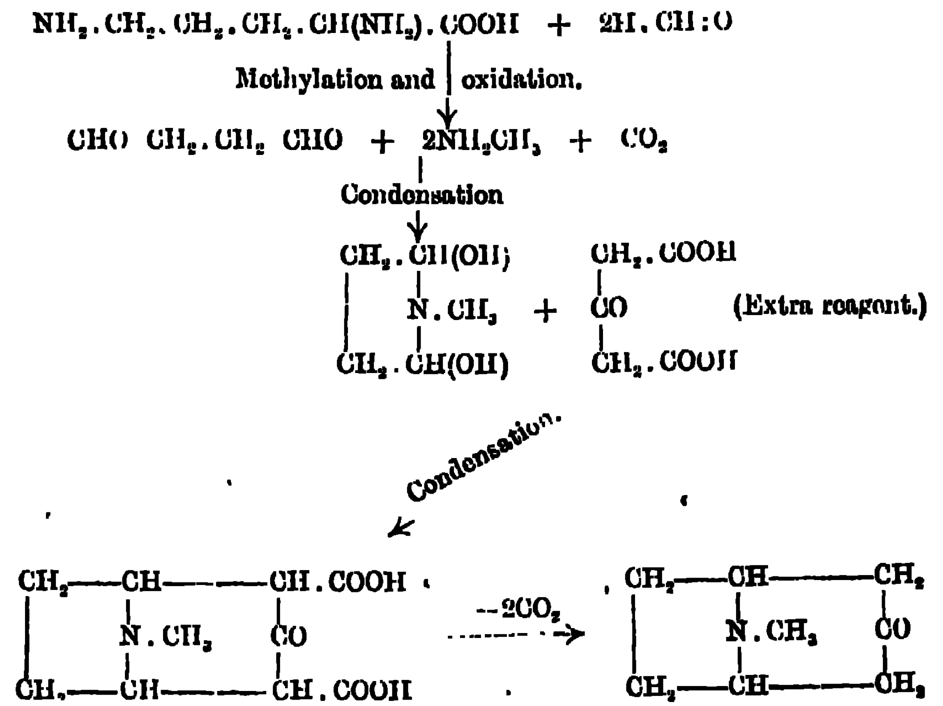


All the dehydrations and rehydrations involved in the process have not been indicated in the formulæ, as by this time the reader is probably sufficiently expert in appreciating the method to dispense with some of the steps. The last stage shown above consists in a reduction of the dihydric alcohol to a hydrocarbon grouping, which accounts for the four extra hydrogen atoms already mentioned. Having thus reached nor-tropinone, methylation with formaldehyde would account for the production of tropinone itself.

Of course the order in the above series of changes might be varied, some of them coming earlier than is shown. The methylation of the nitrogen atom, for example, might take place much sooner than has been assumed.

Robinson[1] has put forward a series of suggestions as to the manner in which many of the familiar alkaloidal skeletons may be produced by using comparatively simple reactions; and his paper should be studied by all who are interested in the question. Unfortunately, it would lose by condensation, so cannot be dealt with here. In it examples are given of possible lines of syntheses in the pyrrolidine, piperidine, quinoline, and isoquinoline groups of alkaloids. Two reactions only are demanded as essential to the formation of the skeletons: the aldol condensation and the similar reaction between carbinolamines [containing the grouping $R_2 : C(OH) . N : R_2$] and compounds containing the radicle : CH . CO.

As an example of the method, we may choose the synthesis of tropinone—


$NH_2.CH_2.CH_2.CH_2.CH(NH_2).COOH$ + $2H.CH:O$
Methylation and oxidation.
CHO $CH_2.CH_2$ CHO + $2NH_2CH_3$ + CO_2
Condensation
(Extra reagent.)
Condensation.
$-2CO_2$

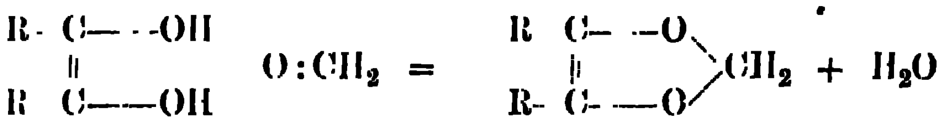
---

[1] Robinson, *Trans.*, 1917, 111, 876.

Robinson's synthesis of tropinone (see p. 124) has shown that reactions of the type required by his views can actually take place in practice under ordinary conditions.

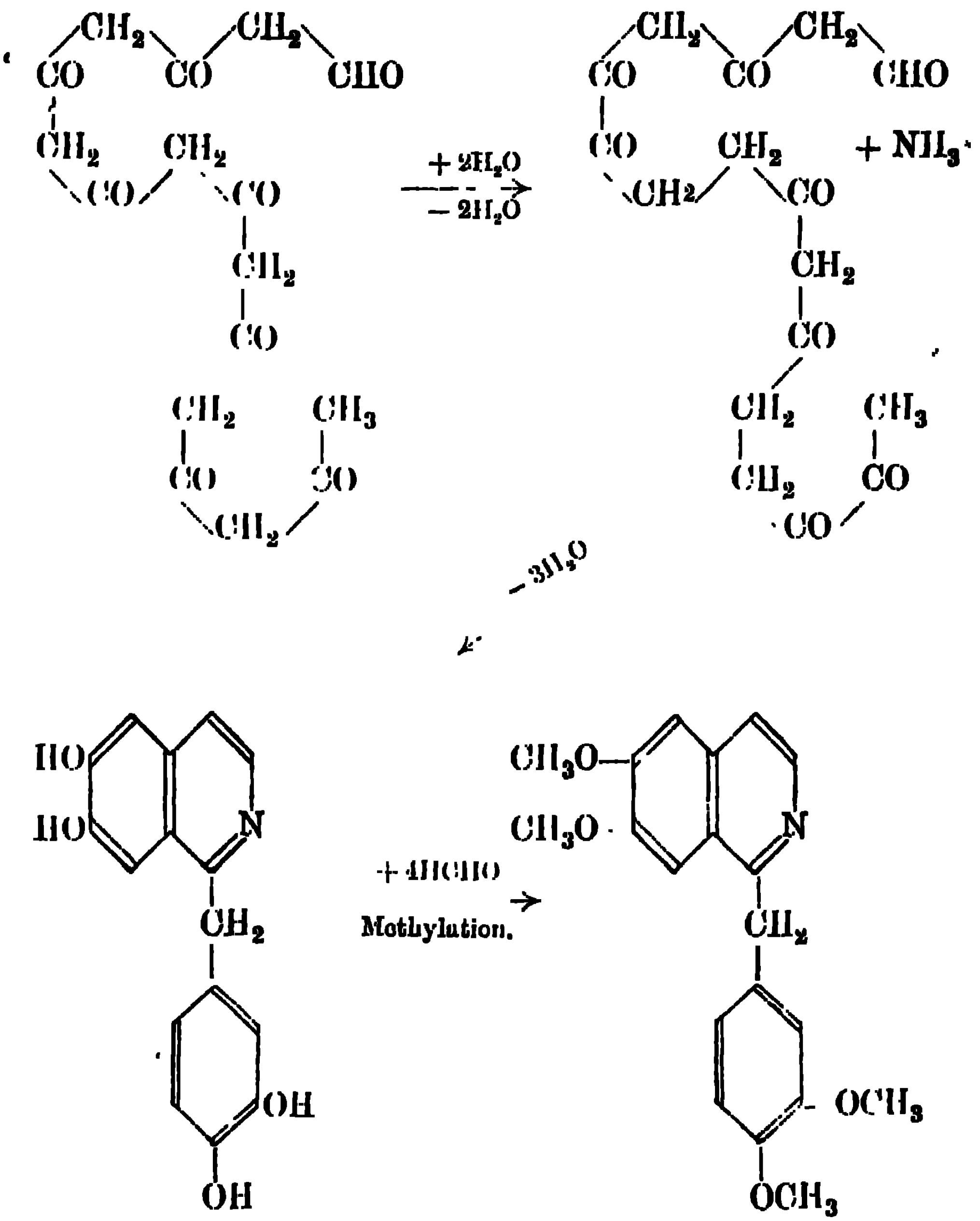
† Returning to the idea that the cellulose chain, *via* the polyketides, affords a source of alkaloid material, an example may be given of the course which the synthesis of papaverine might be expected to take. In the first place, it must be pointed out that by the usual process of dehydration and rehydration, it is possible to pass from the grouping R . CO . CH_2 . CO— to the arrangement R . CH_2 . CO . CO—; and also that the formation of methoxyl radicles and methylene-ether groups may be supposed to take place by the action of formaldehyde:—

$$R.OH + 2CH_2O = R.O.CH_3 + H.COOH$$



$$\begin{array}{l} R\text{—}C\text{—}OH \\ \quad\;\, \| \\ R\text{—}C\text{—}OH \end{array} \quad O:CH_2 = \begin{array}{l} R\text{—}C\text{—}O \\ \quad\;\, \| \\ R\text{—}C\text{—}O \end{array}\!\!>CH_2 + H_2O$$

The outline of the papaverine synthesis is given on the next page.

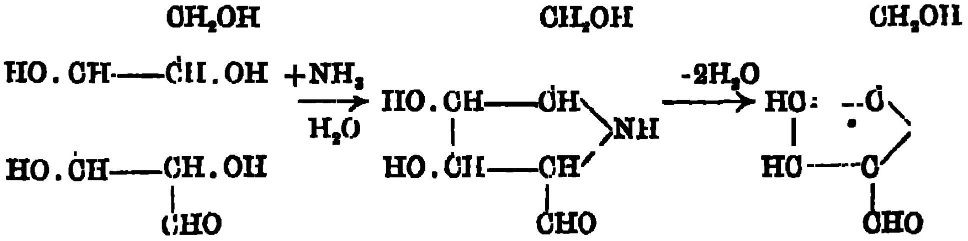


Papaverine.

13. *The Natural Syntheses of Pyrrol Derivatives.*

The importance of the pyrrol compounds from the standpoint of natural processes has already been indicated in an earlier chapter. The assimilative machinery of plants is bound up with chlorophyll; whilst hæmine plays an analogous part in the case of animals: and both these substances are built up on a basis of pyrrol rings. In addition to them, numerous other pyrrol derivatives are known to occur in the products of vegetable and animal metabolism: the pyrrolidine alkaloids and the bile acids are cases in point. It is therefore desirable to indicate here how these substances may be produced by vital reactions.

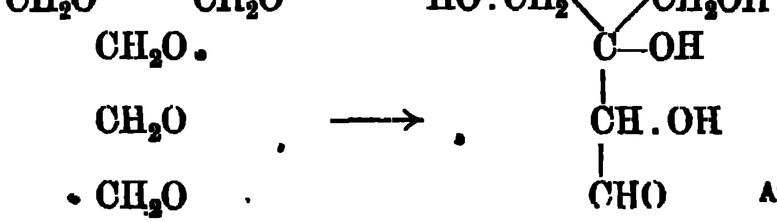
The carbohydrates probably form one source from which materials are drawn for pyrrol syntheses; whilst the nitrogen may be supplied either from ammonia or indirectly from the proteins. Assuming the presence of a sugar and ammonia, the synthesis of a pyrrol derivative may be accounted for by two dehydration reactions thus—



From a pentose, of course, a pyrrol with a single aldehydic side-chain would be produced.

14. *Branched Chains and Terpene Compounds.*

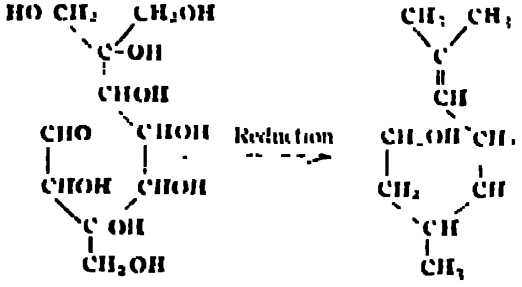
Hitherto we have confined our attention to carbohydrates in which the carbon atoms form a straight chain, but it seems desirable to indicate how forked chains may come into existence, as compounds of this type occur naturally along with straight-chain substances. The formation of apiose may be taken as an example. Its composition is $C_5H_{10}O_5$, and it might obviously be produced by the aldol condensation of five molecules of formaldehyde in the following manner:—



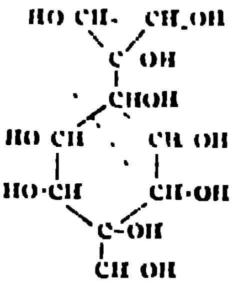
Apiose.

It seems difficult to imagine how apiose can be synthesized naturally in any other way.

But if this be granted, it becomes clear that terpene skeletons might be produced by an extension of the same series of condensations. Two possibilities are open. In the first place, two apiose nuclei may condense together giving the substance (I.) which by reduction may be transformed into an olefinic terpene derivative (II.); and from this, by intramolecular change similar to the geraniol-terpineol rearrangement (see p. 99), a terpene derivative might be formed. Or, alternatively, ten molecules of formaldehyde might condense together to produce a doubly-linked apiose chain (III.) from which terpenes might be formed by reduction.



(I) (II)



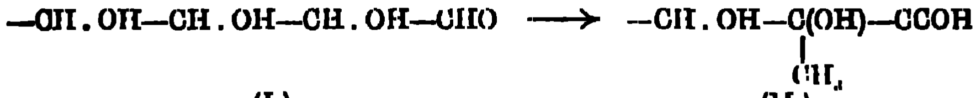
(III)

The particular terpene derivative formed would depend on the stage of oxidation of the original open-chain compound in the second case and also upon the position of the double bonds in the open chain.

Another possible line of synthesis of the terpenes is suggested by the production of a thymol derivative from the condensation products of orcinol and aceto-acetic ester (see p. 256). Since the orcinol and the aceto-acetic ester are both obtainable from polyketide chains, and hence possibly from carbohydrates; and since the thymol compound thus produced may be supposed to be reducible to a terpene, this line of thought leads also from the carbohydrates to the terpene group.

Finally it may be pointed out that a terpene $C_{10}H_{16}$ could be derived from a carbohydrate $C_{14}H_{28}O_{14}$ by the removal of four molecules of carbon dioxide and six molecules of water. In this case it would be necessary to assume as an intermediate compound one of those unsaturated acids which tend to lose their carboxyl radicles spontaneously.

Other reactions which might lead to the formation of a forked chain are the condensation of formaldehyde with a straight sugar chain and subsequent dehydration of the aldol thus produced; or the peculiar rearrangements in the sugar group observed by Kiliani,[1] whereby, under the action of lime-water, the group (I.) is transformed into (II.):



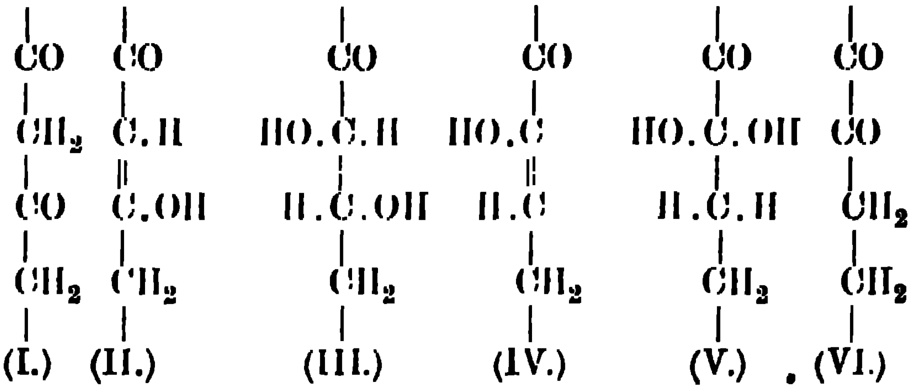
$$-CH.OH-CH.OH-CH.OH-CHO \longrightarrow -CH.OH-\underset{\displaystyle CH_3}{\underset{|}{C}}(OH)-COOH$$

(I.) (II.)

or the analogous benzilic acid change.

15. *The Formation of the Fats.*

For the production of fats in the animal body the carbohydrates absorbed as food form the most probable source. We have already seen that sugars may be converted into polyketide chains by dehydration, so it is not necessary to give these steps. We may commence with the polyketide chain shown in (I.) as an example:—



† If we take as our starting-point the group (I.) and convert it into the enolic form (II.), we can then add a molecule of water on to the double bond to form (III.). This substance could then be dehydrated to produce (IV.), to which water might be again attached, giving (V.), in which two hydroxyl groups are attached to the same carbon atom. This compound would lose a molecule of water, leaving (VI.).

† A comparison of the formulæ (I.) and (VI.) shows that the whole process implies a wandering of the hydrogen atoms to the lower end of the chain, and a corresponding migration of the oxygen atoms to the other. This purely theoretical series of actions could then be repeated, and the final result would

---

[1] Kiliani, *Ber.*, 1884, 17, 1302; 1905, 38, 2668; 1908, 41, 158, 469.

be a loss of carbon dioxide from one end of the chain, and a building up of an aliphatic chain at the other end. Some such process may take place in the living organism during the formation of oils or fats,* and the liberation of carbon dioxide in respiration would be explicable in the same way.

Evidence in favour of this conception of the formation of fats from carbohydrates is obtained when the results of the reverse process are examined. In the disease pentosuria, the body fats are broken down and converted into sugars. Now, if this process involved the decomposition of the fat, with subsequent assimilation in the organism, then a synthesis of the pentose and, finally, its excretion, we should expect to find that the inactive fat had been converted into an *optically active* sugar owing to the intervention of the asymmetric components of the body tissues, etc. On the other hand, if the fat is converted direct into the sugar by the converse of the process sketched above—*i.e.* if the process involves a mere passage from Stage VI. to Stage I.—then, owing to the continual formation of enolic forms and consequent loss of asymmetry, the products of the fatty decomposition would not be active. In actual practice it is found that the arabinose excreted by patients suffering from pentosuria is the racemic form[1] of the compound; and this notwithstanding the fact that the organism is quite capable, even in that state, of decomposing *l*-arabinose if this sugar be given in food. It seems evident, therefore, that the arabinose excreted by such patients cannot have passed through the ordinary channels, but must have been produced directly from fat by some simple reaction such as is shown above Further the occurrence of aceto-acetic acid and acetone along with sugar in the urine of patients suffering from diabetes proves that polyketide derivatives make their appearance during the disease.

16. *Syntheses and Degradations of the Proteins.*

In the foregoing sections we have dealt very fully with the carbohydrates and their possible mutations; so that it will be necessary to devote only a small space to the proteins, that second great class of up-grade products of the vital machinery. Fischer's researches on the polypeptides[1] leave little doubt that the protein molecules contain long chains of amino-acids coupled together in the form of amides; and it remains to suggest methods whereby such substances could be synthesized from simple materials within the living organism.

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* Or wax in the case of bees.

[1] Neuberg, *Ber.*, 1900, 33, 2243.

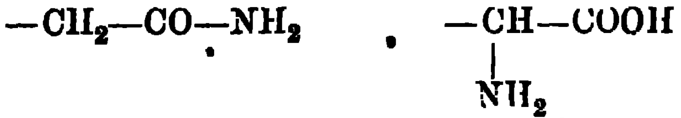
As in the case of the carbohydrates, our knowledge of the initial steps in the process is incomplete. Nitrates appear to be assimilated by the plant and reduced to nitrites; but uncertainty exists as to the further fate of the nitrite when it has been formed. The most suggestive experiments on the subject appear to be those of Baudisch.[2] On exposing potassium nitrate to diffused daylight, he found that it was reduced to potassium nitrite. Under the same conditions, potassium nitrite, when mixed with formaldehyde or methyl alcohol, became converted into hyponitrite and then, by the action of more methyl alcohol, was changed into the potassium salt of formohydroxamic acid:—

$$CH_3OH + KNO_2 = HO.CH:N.OK + H_2O$$

Prolonged exposed to light resulted in a further reduction, ammonia being formed.

According to Baudisch, ammonia in plants is oxidized by oxidases or by ultra-violet light, and the resulting product combines with formaldehyde to form aci-nitromethane which, being a reactive substance, takes part in vegetable syntheses.

If we assume the presence of ammonia and carbohydrates, however, the further reactions may be formulated in other ways. We may postulate that the first step in the synthesis of the proteins is the production of an amide. We are faced with a certain difficulty; for it is clear that an inversion of some kind must take place in order to convert the group (I.) into the group (II.), which entails the transference of the nitrogen atom from one carbon atom to the next



$$-CH_2-CO-NH_2 \quad , \quad -\underset{\underset{\displaystyle NH_2}{|}}{CH}-COOH$$

(I.) (II.)

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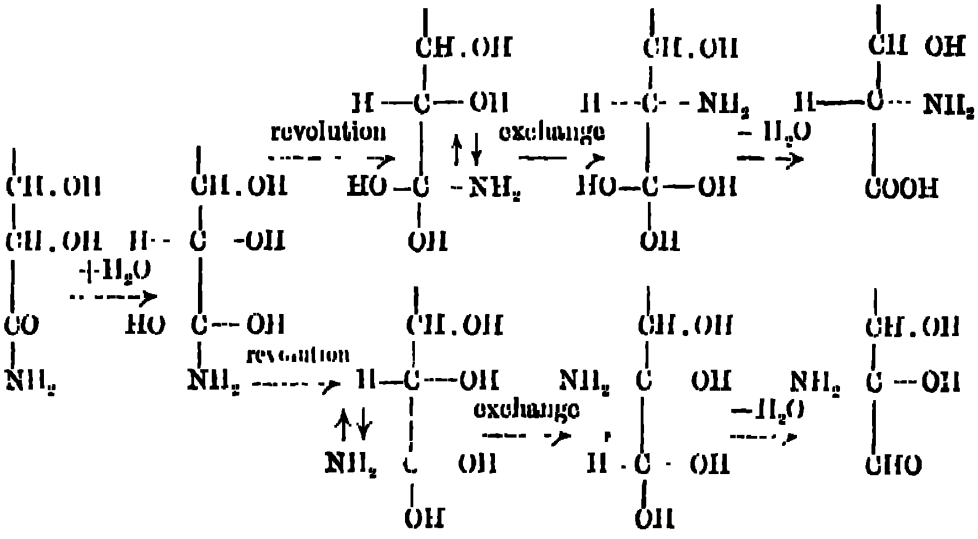
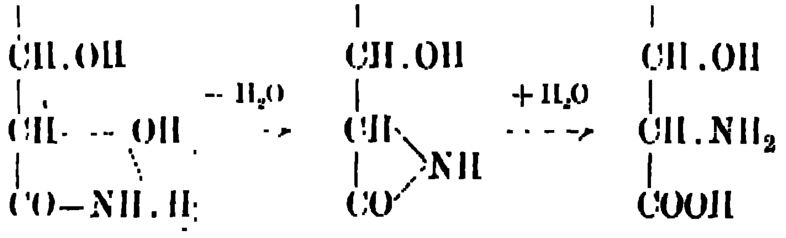
[1] See p. 184.

[2] Baudisch, *Ber.*, 1911, 44, 1009.

†Such transferences are quite possible on lines with which we are already familiar. The following symbols show the application of the pinacone rearrangement to the problem—



Another method by which the transference of the nitrogen atom to the neighbouring carbon might be accomplished is by the temporary production of a three-membered ring which, as soon as formed, might open up again in a new place. In this way the reaction is reduced to the simple subtraction and readdition of a molecule of water—



The production of the original amido radicle may be attributed to the formation and partial hydrolysis of a cyanhydrin of the sugar; for hydrocyanic acid is known to be formed in plants in quantities sufficient to yield the required cyanhydrins.

Much more probable than either of the above suggestions is the following, which is based upon an observation of de Jong[1] in the case of pyruvic acid. When ammonium pyruvate is mixed with pyruvic acid the reaction takes the following course. In the first place the two pyruvic molecules (I.) react with ammonia from the ammonium salt to form an imino compound (II.). This substance then loses water, and forms the lactone (III.). A molecule of water is then taken up and carbon dioxide is split off, yielding the substance (IV.), which immediately eliminates another molecule of water, producing *a*-acetyl-amino-propionic acid (V.)—

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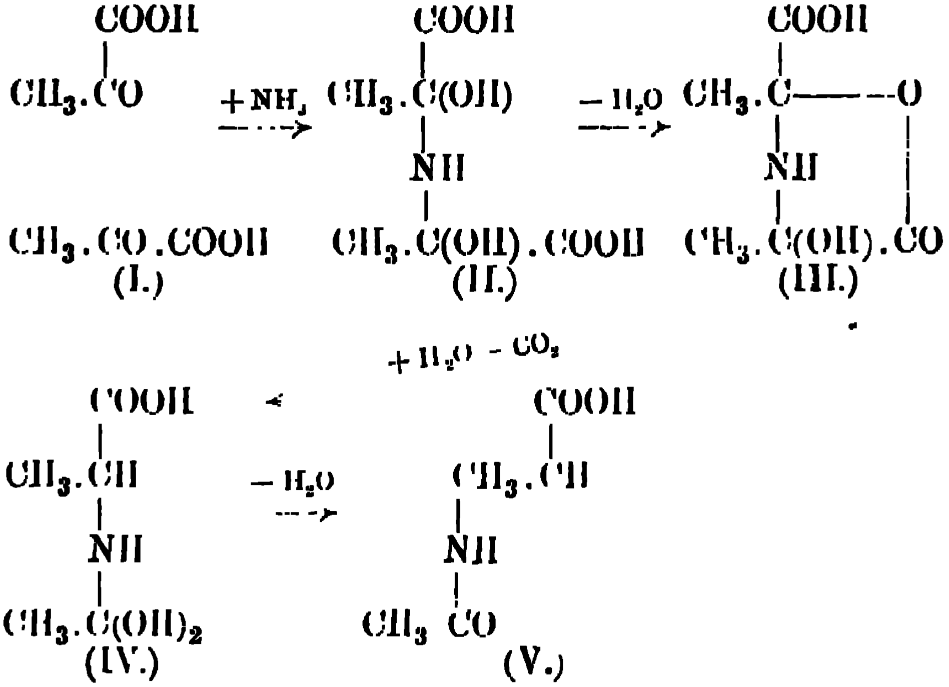
[1] De Jong, *Rec. trav. chim.*, 1900, 19, 259; 1904, 23, 131.



Now it will be seen that this reaction leads to the formation of the type of amino-acid most common among the protein derivatives—the *a*-amino-acid; for the acetyl group could easily be hydrolysed away by enzyme action.

The application of this to more complex cases is not difficult. It will be remembered that in the section dealing with the formation of fats it was pointed out that a very simple process would lead from the carbohydrates of the type R—CH.OH—CH.OH—CH.OH→CH.OH—CHO to derivatives of the structure R—CH_2—CH_2—CO—CO—COOH. Oxidation of the latter would yield homologues of pyruvic acid, the number of carbon atoms in the group R depending upon the length of the carbohydrate chain which serves as a raw material. Once these pyruvic acid derivatives have been produced, there is no reason why they should not undergo de Jong's reaction and form the corresponding *a*-amino-acids;

and in this way the raw materials for polypeptide and protein syntheses might be produced.[1]

In connection with the protein syntheses, another point of interest arises, though it must be classed as a purely speculative one. If two molecules of formaldehyde could be induced to condense together in the following manner, keten would be formed; and from this, by polymerization, chains of polyketides might be formed:—

$$H_2C:O + H_2C:O = H_2O + CH_2:C:O$$

Now, similarly, we might devise a synthesis in the nitrogen group—

$$NH_3 + (HO)_2C:O = 2H_2O + NH:C:O$$

This compound is, of course, isomeric with cyanic acid.

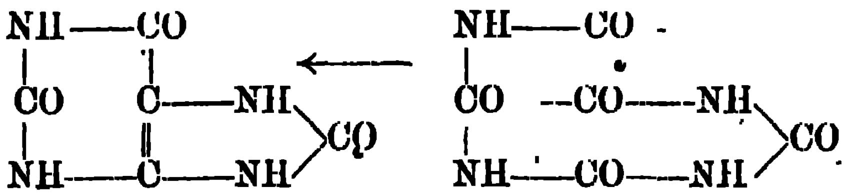
† For present purposes, however, our interest in it arises from the fact that it is obviously the nitrogen analogue of keten—

$$CH_2:C:O \qquad\qquad NH:C:O$$

and, from this similarity, we may term the compound aziketen. Now just as keten can polymerize to long chains which then add on water to form polyketides, so aziketen should polymerize and hydrate in order to produce the simplest type of polypeptide—

$$NH_2-CO-NH-CO-NH-CO-NH\quad COOH$$

† It is at this point desirable to bring the matter into touch with actual practice. If we examine the formula of uric acid, it requires no great stretch of imagination to recognize that the purine compounds are derivatives of this type of polypeptide, probably produced from the open-chain compound by reduction accompanied by ring formation—



Thus the break-down of the sugars into the various aromatic and pyrone derivatives would find its analogue in the formation of the uric acid derivatives from the proteins.

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[1] For other suggestions see Haas and Hill, *Chemistry of Plant Products*, p. 333 ff.

† Another suggestion as to the production of purine derivatives by vital processes may be put forward. In the breakdown of proteins, amino-acids of the type $R-CH(NH_2)-COOH$ are formed. Now in the oxidation of these, it is possible that the hydrocarbon chain R is burned away first, leaving behind the potential $-NH.CO-$ portions, which may then unite to form uric acid and its derivatives.

17. *Conclusion.*

In this chapter an attempt has been made to sketch certain methods by which natural products may possibly come into existence in the organism, but it cannot be too strongly emphasized that they are intended merely as suggestions and not as dogmatic attempts to settle the problems involved. If they have brought to the notice of the reader the questions which arise in this branch of chemistry and have inspired any desire to go further into the matter, they have amply fulfilled the object for which they were written. We are at present far from a definite knowledge of how the vital machine carries out its work; but if the ideas collected in the present chapter induce the reader to speculate for himself on the subject, he will find a most fascinating field open to him.

One point which certainly comes into prominence in the foregoing pages is the fact that, by a series of hypothetical dehydrations and rehydrations, it is easy to see how very different types of grouping might be produced. A system which is capable of accounting for the production of such widely varying materials as benzene derivatives, pyrrols, pyridine derivatives, pyrones, anthocyanins, fats and alkaloids has evidently something more than mere plausibility behind it. We are not yet able to carry out these changes in the laboratory, except in the case of the polyketide derivatives; but it will be surprising if sooner or later some experimental evidence is not found to bear out much that has been advanced in the preceding sections.

† Should the reader wish to pursue speculations in this field the following questions may serve to guide his attention

to some hitherto unsolved problems. The fatty acids of the acetic series are quite common in nature, whilst their hydroxy-derivatives—with the exception of lactic acid—are hardly represented at all. Why should this be so? Why do all the important sugars and starches contain a chain of five or six *or a multiple of five or six* carbon atoms? Why are the majority of the amino-acids obtained from the proteins the *α*-amino-acids? Why are the ortho- and meta-derivatives so strongly represented among naturally occurring benzene derivatives, whilst the majority of the terpenes are derived from *para*-cymene?

† In the case of such broad generalities there must surely be some simple solution. The curious thing is—not that the answers to these questions are omitted from the ordinary text-books, but rather that the questions do not appear to have suggested themselves to the writers at all.

CHAPTER XI

TRIVALENT CARBON

1. *Triphenylmethyl.*

ANYONE who glances through the journals of the chemical world for the last few years must be struck by the enormous production of new compounds which is at present going on; and, if he reflects at all, he will be driven to ask himself what criterion should be applied in order to distinguish the really important substances from what we may term the by-products of synthetic chemistry. Clearly the only fate which can overtake the majority of these new compounds is that their dossiers will be "neatly tucked away in Beilstein, the Abstracts published by the various Chemical Societies, or in other equally convenient depositories of information." They will remain at best in a dormant condition, waiting the time when some *Analogie-arbeit* necessitates a knowledge of their properties. On the other hand, those new bodies which have any interest apart from their melting-points soon become centres of new research; and the more important of them usually lead to investigations extending far beyond the constitution and properties of the original compound. For example, the researches which more than a generation ago took their rise in the constitution of aceto-acetic ester have not yet reached their final stages.

This ramification of interest has seldom been so strongly marked within recent years as in the case of the substance termed triphenylmethyl; and it is the rapid extension of the field of research in this division of the subject which makes any treatment of the triphenylmethyl problem difficult. In the present chapter, it will be necessary to confine ourselves as far as possible to the narrow question of the constitution of triphenylmethyl and only to touch lightly upon the wider questions which are closely bound up with it.

The discovery of triphenylmethyl resulted from an attempt to prepare hexaphenyl-ethane, which was made by Gomberg[1] in 1900. He allowed "molecular" silver to act upon triphenyl-bromo-methane, and obtained a compound which he naturally supposed to be hexaphenyl-ethane; for the reaction would normally have taken the course expressed in the formulæ below—

$$2(C_6H_5)_3C \,.\, Br + 2\,Ag = (C_6H_5)_3C-C(C_6H_5)_3 + 2\,AgBr$$

On analysis, however, the substance is found to have about 6 per cent. too little carbon to agree with the hexaphenyl-ethane formula; and further examination showed that it could not be a hydrocarbon at all, but must contain oxygen.

This oxygen might have been introduced in either of two ways: it might have been imported through the silver used in the reaction: or it might have been derived from the air. The experiments were therefore repeated, other metals, such as zinc and mercury, being used instead of silver; and still the resulting substance was found to be oxygenated. From this it was clear that atmospheric oxygen was the source of the oxygen in the end-product; and further experiments were made in which precautions were taken to exclude air from the apparatus. The end-product in this case differed from that which had previously been obtained; and on analysis it was found to have the composition corresponding to hexaphenyl-ethane.

An examination of its properties, however, brought Gomberg to the conclusion that the substance which he had obtained could not be hexaphenyl-ethane; for he had expected that that body would be an extremely stable compound, whereas his synthetic hydrocarbon was very reactive.

At this point we may give a *résumé* of the chief properties of the hydrocarbon. When first prepared, it is a colourless crystalline solid, which dissolves with great readiness in most organic solvents, giving yellow solutions. Even at zero it reacts with iodine to form triphenylmethyl iodide. Exposure to the air even for a short time is sufficient to transform it into a peroxide; and Gomberg[1] has been able to prove that this same peroxide can be produced by the action of sodium peroxide on triphenyl-chloro-methane (but not by the spontaneous oxidation of triphenylmethyl chloride or of triphenyl carbinol under the same conditions). From this we may deduce that the peroxide has the constitution—

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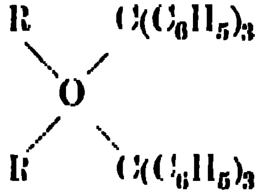
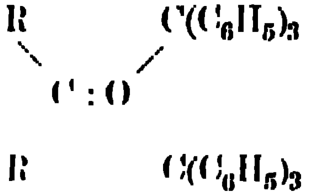
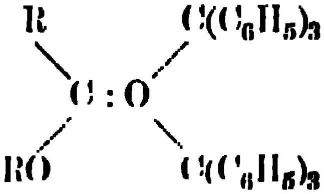
[1] Gomberg, *J. Amer. Chem. Soc.*, 1900, **22**, 757; *Ber.*, 1900, **33**, 3150.

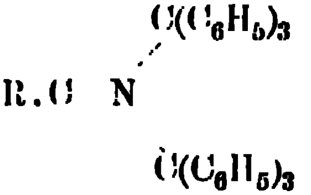
$$(C_6H_5)_3C—O—O—C(C_6H_5)_3$$

The hydrocarbon forms double compounds[2] with ethers, esters, ketones, nitriles, or aromatic hydrocarbons (and amylene), the composition of these substances corresponding to one molecule of ether (or of the other substances) plus one molecule of hexaphenyl-ethane. Gomberg ascribed the formation of the oxygenated derivatives to the change of the oxygen from the divalent to the quadrivalent condition, and formulated the constitution of the substances generally as derivatives of the following types:—









The fact that these substances are actually compounds and not simply mixtures in which the ether or other body is held mechanically is proved by the fact that similar compounds are formed with carbon disulphide and chloroform, and these latter bodies can be heated to 110° C. in a stream of carbon dioxide without giving up their full content of chloroform or disulphide. With sodium, the hydrocarbon forms a brick-red compound[3] having the formula $(C_6H_5)_3C . Na$ which is very reactive.

There is one further point to which we must draw attention though it does not directly concern the hydrocarbon. It has been shown[1] that the halogen salts, such as triphenylmethyl chloride $(C_6H_5)_3C.Cl$, and triphenylmethyl bromide $(C_6H_5)_3C.Br$, when dissolved in solvents such as liquid sulphur dioxide which have strong dissociating power, have conductivities very nearly equal to that of methylamine hydrochloride. This proves that in the yellow solutions obtained in this way, the compounds are split up into two ions, one of which must be $(C_6H_5)_3C$.

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[1] Gomberg, Ber., 1900, 33, 3150.

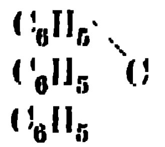
[2] *Ibid.*, 1905, 38, 1333, 2447.

[3] Schlenk and Marcus, *Ber.*, 1914, 47, 1664.

From the data which we have given in the preceding paragraphs, it is clear that the problem of the constitution of Gomberg's synthetic hydrocarbon opens up a wide field for speculation; and numerous attempts have been made in recent years to discover the solution. Four views have at one time or another gained a certain amount of support, and we shall deal with these in turn in the following sections.

2. *The Trivalent Carbon Hypothesis.*

The reactions of his synthetic hydrocarbon—which we may for the sake of convenience term triphenylmethyl—led Gomberg[2] to put forward the view that the substance contained one carbon atom attached to three phenyl radicles, but having no fourth radicle attached to it:—



$$\begin{matrix} C_6H_5 \diagdown & \\ C_6H_5 - & C \\ C_6H_5 \diagup & \end{matrix}$$

The fourth valency of the carbon atom may be supposed to be free, or to be absorbed by the residual valency of the three phenyl groups. This conception of a trivalent carbon atom is really not so extraordinary as it seems; for we might consider that ethylene derivatives contain two adjacent carbon atoms of this type, instead of writing their structural formulæ as we usually do with a double bond between the two unsaturated carbons.

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[1] Walden, *Ber.*, 1902, **35**, 2018; Gomberg, *ibid.*, 2045. Compare Gomberg, *Ber.*, 1905, **38**, 1342.

[2] Gomberg, *J. Amer. Chem. Soc.*, 1900, **22**, 757; *Ber.*, 1900, **33**, 3150.

In favour of this constitutional formula for triphenylmethyl we may urge the evidence derived from the reactions of the substance with iodine and with oxygen, both of which can be expressed quite simply :—

$$\begin{array}{c}(C_6H_5)_3C\\ \\(C_6H_5)_3C\end{array} + \begin{array}{c}I\\|\\I\end{array} = \begin{array}{c}(C_6H_5)_3C.I\\ \\(C_6H_5)_3C.I\end{array}$$

$$\begin{array}{c}(C_6H_5)_3C\\ \\(C_6H_5)_3C\end{array} + \begin{array}{c}O\\\|\\O\end{array} = \begin{array}{cc}(C_6H_5)_3C & O\\ & |\\(C_6H_5)_3C & O\end{array}$$

And we might also adduce the simplicity of the formulæ for the double compounds of triphenylmethyl with ethers, ketones, nitriles, etc.

All that this amounts to, however, is that we can express these reactions in a straightforward manner on the assumption of trivalent carbon.* If we can express them equally convincingly by means of a formula containing only quadrivalent atoms, then we should be entitled to reject the trivalent carbon view as adding an unnecessary assumption to our usual ones.

But there are facts which conflict with the trivalent carbon view. Gomberg and Cone[1] have shown that the three phenyl radicles do not possess identical properties, as they should do if the substance actually had the triphenylmethyl structure. We need only outline their proof here, as we shall have to return to it in a later section. By subjecting para-rosaniline to Sandmeyer's reaction they obtained tri-*p*-bromo-triphenyl carbinol, which, by the action of hydrochloric acid, was transformed into tri-*p*-bromo-triphenylmethyl chloride—

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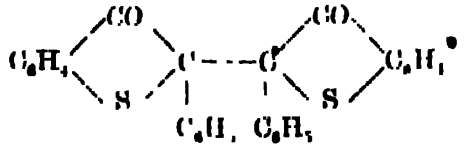
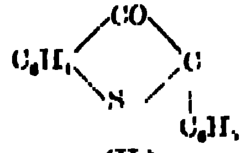
* Kalb and Bayer (*Ber.*, 1913, **46**. 3879) state that 2, 2'-diphenylthioindigo white (I) dissociates in solution into two free radicles each containing trivalent carbon and having the structure (II.)—

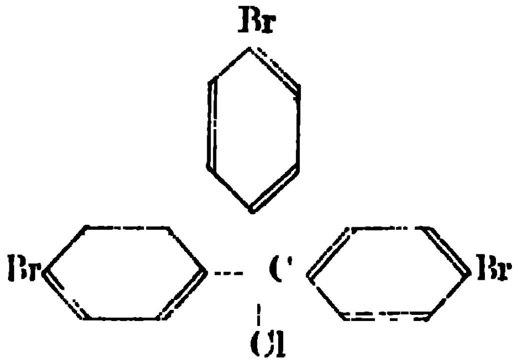


(I.)

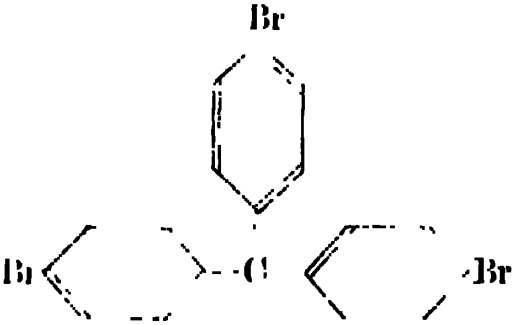


(II.)

[1] Gomberg and Cone, *Ber.*, 1906, **39**. 3274.

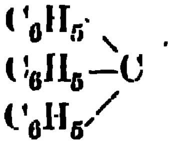


When this substance was treated in the usual way with silver, it gave a substance analogous to triphenylmethyl. This new compound formed a peroxide just as triphenylmethyl does, and therefore (if the trivalent carbon idea be correct) we may safely assume that it is tri-*p*-bromo-triphenylmethyl—



Now the tri-*p*-bromo-triphenyl chloride was sealed up in an air-free flask with excess of molecular silver, and the whole was shaken for a considerable time. At the end of this, it was found that the silver had removed all the chlorine (reaction of triphenylmethyl formation), but in addition it had abstracted one atom of bromine from the ring of one of the phenyl groups. Since there was excess of silver present, if all the three phenyl radicles had identical properties we should expect that they would yield up their bromine simultaneously. Further, the new compound produced by the elimination of bromine was not a peroxide similar to that formed by triphenylmethyl, nor did it yield such a peroxide when exposed to air. The experiments were repeated with other halogen derivatives of triphenylmethyl, and led in those cases to similar results. It is thus shown: (1) That the substitution of three bromine atoms in the position para to the "trivalent" carbon of triphenylmethyl in no way interferes with the activity of the substance;

(2) further action of silver eliminates only one of the three bromine atoms, so that one nucleus differs from the other two. From (1) the complete analogy between triphenylmethyl and its tribromo-derivative is clear; and hence we are entitled to draw the conclusion that the inference in (2) is valid also for the parent hydrocarbon. But if in triphenylmethyl we have one phenyl nucleus endowed with properties not shared by the other two, it is evident that a symmetrical formula—



cannot give a true representation of the substance's properties.

A further complication is introduced into the problem by a consideration of the molecular weight of triphenylmethyl in solution. If we assume that the free radicle triphenylmethyl, $C_{19}H_{15}$, is present, then the molecular weight should be 243; whereas if hexaphenyl-ethane is formed, its molecular weight ought to be 486. Actual experiments show that in naphthalene at 80° C. the molecular weight is 414; whilst in benzene near 0° C. it appears to be 480–485.[1] These results suggest that under certain conditions the hexaphenyl-ethane dissociates to some extent into triphenylmethyl radicles.

This idea has received further support from the work of Schlenk[2] on other compounds of the triphenylmethyl type. Thus the molecular weight of phenylxanthyl (I.) is 257 for the monomolecular (trivalent carbon) form and 514 for the bimolecular (quadrivalent carbon) substance. The actual value found in benzene by the ebullioscopic method is 279; pointing to the probability that 82 per cent. of the substance exists in the solution as a free radicle whilst only 18 per cent. of the bimolecular form is present. Again, phenyl-biphenyl-*a*-naphthylmethyl (II.) should have a molecular weight of 369 for the free radicle and 738 for the bimolecular form. In boiling benzene the actual value determined was 362, which proves that the substance exists under these conditions as the free radicle.

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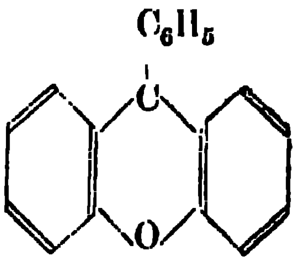
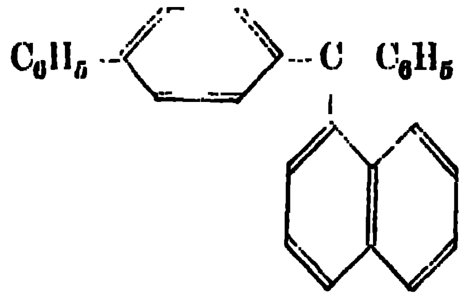
[1] Gomberg and Cone, *Ber.*, 1904, 37, 2087; 1906, 39, 3274.

[2] Schlenk, *Annalen*, 1912, 394, 178.



(I.)



(II.)

It has been shown by Piccard[1] that the colour of triphenylmethyl solutions in ether deepens on dilution,* which suggests that the lowering of the concentration is accompanied by an increase in the dissociation of the bimolecular form; whilst Gomberg and Schoepfle[2] have studied the influence of the constitution of the triarylmethyls upon their degree of dissociation.

The foregoing evidence is thus somewhat confusing. On the one hand, it proves that triphenylmethyl cannot be symmetrical in structure; and on the other side it establishes the fact that the triarylmethyl derivatives do actually exist in solution in the form of free radicles. It is clear that we must seek further if we are to find a satisfactory solution of the problem.

3. *The Hexaphenyl-ethane Hypothesis.*

When Gomberg's hydrocarbon was first prepared, its properties were found to be so different from what had been expected of hexaphenyl-ethane that the latter structure was at once dismissed as incapable of giving a proper representation of the reactions of the new substance; but as time went on, and more information with regard to the properties of the more highly phenylated ethanes was acquired, it seemed as if the earlier view had been rather hasty, and that there was a certain amount of probability in the idea that Gomberg's compound was, after all, merely hexaphenyl-ethane.

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[1] Piccard, *Annalen*, 1911, 381, 347; compare Hantzsch, *ibid.*, 384, 185; 1913, 398, 379.

* Normally, of course, dilution has no influence on absorption power since the light-ray passes through the same number of molecules in either concentrated or dilute solutions, provided that the thickness of the layer is kept directly proportional to the degree of dilution. This is known as Beer's Law.

[2] Gomberg and Schoepfle, *J. Amer. Chem. Soc.*, 1917, 39, 1652.

For two years, however, this view was kept in abeyance, owing to the fact that Ullmann and Borsum[1] had synthesized a substance which they regarded as hexaphenyl-ethane. This body was obtained by reducing triphenyl carbinol; and its properties corresponded to some extent with those which had been anticipated for hexaphenyl-ethane. In 1904, however, Tschitschibabin[2] established the constitution of this supposed hexaphenyl-ethane, proving it to be a compound of the following structure:—

$$(C_6H_5)_3C - C_6H_4 \quad CH(C_6H_5)_2$$

The removal of the supposed hexaphenyl-ethane from the literature thus left open the possibility that Gomberg's triphenylmethyl really had the hexaphenyl-ethane structure, and Tschitschibabin[2] put this suggestion forward, basing his views on the following considerations.

In the first place, we have to account for the reactivity of triphenylmethyl, and show why a compound of the hexaphenyl-ethane structure should be reactive. Tschitschibabin pointed out that an accumulation of electro-negative atoms or radicles in a molecule tends to make it much less stable. For example, Zincke showed that the accumulation of chlorine atoms in the phenol molecule leads to its degradation into simpler substances. Again, spatial factors sometimes come into play and cause a saturated substance like trimethylene to behave as if it were an unsaturated hydrocarbon. These considerations show that we must be prepared for certain anomalies and must beware of judging problems of constitution on too rigid lines. Further, it is not necessary to assume an unsaturated structure for triphenyl-methyl merely in order to account for its ready reaction with oxygen to form a peroxide, for Gomberg[3] himself has shown that the fully saturated analogue triphenyl-iodomethane reacts in a similar manner. Nor is this all; for when we examine more carefully the behaviour of the highly phenylated ethane derivatives we shall find that they are by no means so stable as analogy would lead us to expect. Tschitschibabin[1] has proved that even below its melting-point pentaphenyl-ethane is attacked by air; at a temperature of only 150° C. hydrochloric acid in benzene solution acts on it so powerfully that the bond between the two ethane carbon atoms is broken, and such products as tetraphenyl-ethane, triphenyl-methane, and triphenyl-chloro-methane, are formed; whilst Cone and Robinson[2] found that the action of phosphorus pentachloride in boiling benzene broke down the pentaphenyl derivative into triphenylmethyl chloride.

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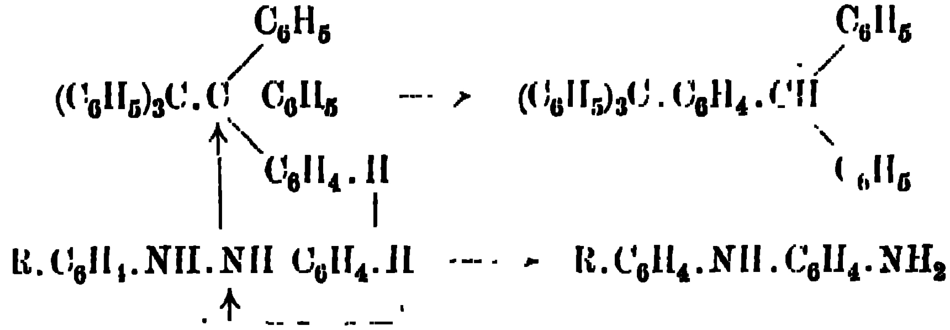
[1] Ullmann and Borsum, *Ber.*, 1902, 35, 2877; Gomberg, *ibid.*, 3914.

[2] Tschitschibabin, *Ber.*, 1904, 37, 4709.

[3] Gomberg, *Ber.*, 1902, 35, 1836.

Against the hexaphenyl-ethane hypothesis we may adduce several arguments. In the first place, triphenylmethyl is a colourless solid, but its solutions are deep yellow in tint: no ordinary benzenoid derivative is known which behaves in this way. Stronger evidence is to be found in the work of Gomberg (mentioned in the previous section), by which he showed that one phenyl group had properties different from those of the others The ordinary hexaphenyl-ethane formula gives no indication of this. Thirdly, Gomberg[3] has proved that his hydrocarbon can easily be converted into that which was obtained by Ullmann and Borsum. On the hexaphenyl-ethane hypothesis, this reaction would run the following course, which is parallel to that which is taken in the semidine change—



$$(C_6H_5)_3C.C\begin{cases}C_6H_5\\C_6H_5\\C_6H_4.H\end{cases} \longrightarrow (C_6H_5)_3C.C_6H_4.CH\begin{cases}C_6H_5\\C_6H_5\end{cases}$$

$$R.C_6H_4.NH.NH\,C_6H_4.H \longrightarrow R.C_6H_4.NH.C_6H_4.NH_2$$

But Jacobson,[4] the greatest authority on the benzidine and semidine changes, regards such a change in the triphenylmethyl series as most unlikely. Lastly, we have already seen that one of the most marked characteristics of triphenylmethyl is its capacity for forming double compounds with solvents; but no such property seems to be possessed by compounds analogous to hexaphenyl-ethane.

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[1] Tschitschibabin, *Ber.*, 1907, **40**, 367.

[2] Cone and Robinson, *Ber.*, 1907, **40**, 2160.

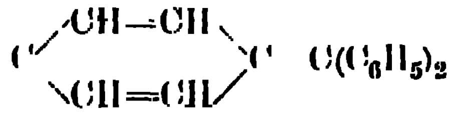
[3] Gomberg, *Ber.*, 1902, **35**, 3918; 1903, **36**, 376.

[4] Jacobson, *Ber.*, 1904, **37**, 196.

From the foregoing paragraphs, it is clear that most of the arguments both in favour of and against the hexaphenyl-ethane view depend to some extent upon analogy; and we must be careful not to lay too much stress upon them unless we are satisfied that the analogies really hold good. If we rule out the arguments based upon what a compound "ought" to do, it will be seen that the evidence remaining—Gomberg's differentiation between the phenyl nuclei—tells against the hexaphenyl-ethane hypothesis.

4. *Quinonoid Hypotheses.*

If we reject the two hypotheses which we have dealt with in the preceding sections, it is clear that we have still a third possibility open to us: for both the triphenylmethyl view and the hexaphenyl-ethane explanation were based on the assumption that the phenyl nuclei in triphenylmethyl were benzenoid in character; so that by assuming a quinonoid structure for the substance we shall arrive at totally different types of formulæ. The quinonoid conception of triphenylmethyl was put forward very early in the compound's history by Kehrmann[1]—



This suggestion, involving as it does the assumption of a divalent carbon atom, meets with little approval at the present time; and since other formulæ of the quinonoid type have since been suggested which do not necessitate such a postulate, we need not deal further with this one.

In 1903 Heintschel[2] put forward a new suggestion. On his hypothesis, the first step in the synthesis of triphenylmethyl is the conversion of triphenyl-chloro-methane into a desmotropic form in which the chlorine atom has been shifted into a position para to the methane carbon atom—

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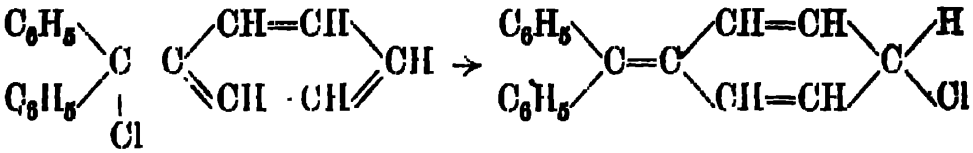
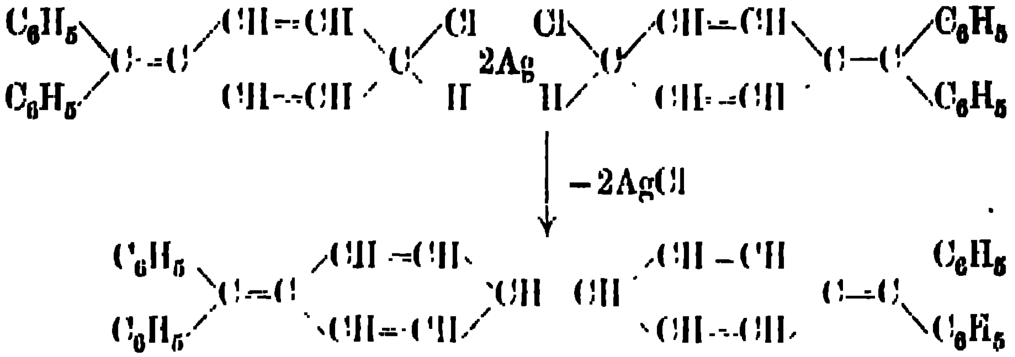
[1] Kehrmann, *Ber.*, 1901, **34**, 3818; see also Norris and Sanders, *Am. Chem. J.*, 1901, **25**, 117; and Gomberg, *Ber.*, 1902, **35**, 1824.

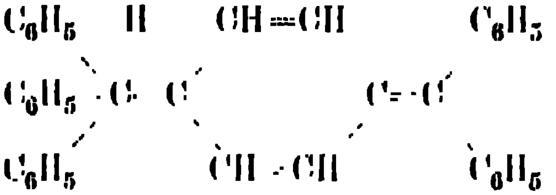
[2] Heintschel, *Ber.*, 1903, **36**, 320, 579.



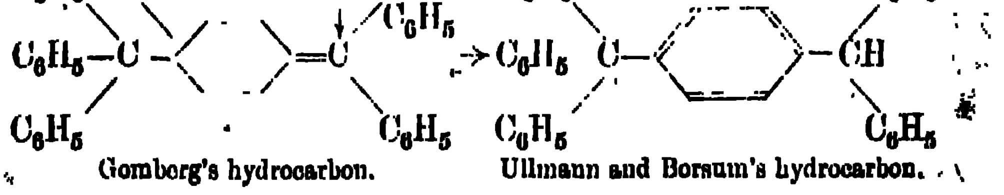
By the action of metals, two chlorine atoms are withdrawn from two molecules of the chloro-compound, and in this way triphenylmethyl is produced—



An examination of Heintschel's formula will show that it contains two quinonoid phenyl nuclei. Jacobson[1] proposed to modify this, making only one phenyl group quinonoid, as shown below—



This view makes triphenylmethyl a derivative of a substance approaching the quinole type; and as the reactivity of the quinoles is quite abnormal, we might expect considerable reactive power from a body having the structure proposed by Jacobson. The change of the Gomberg hydrocarbon into the substance prepared by Ullmann and Borsum can also be easily explained on this hypothesis, as the wandering of a single hydrogen atom is sufficient to account for the isomerization—



Gomberg's hydrocarbon. Ullmann and Borsum's hydrocarbon.

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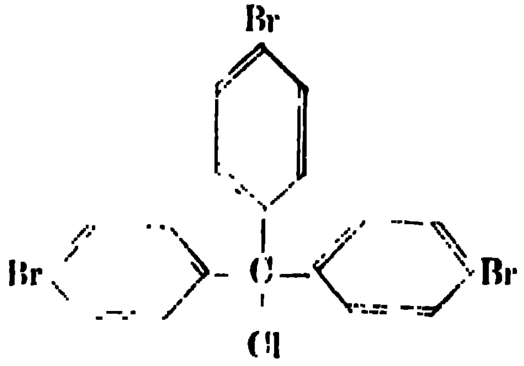
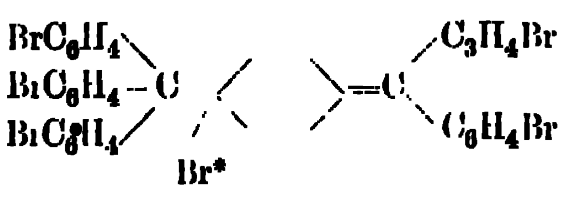
[1] Jacobson, *Ber.*, 1904, 37, 196.

The Jacobson formula helps us to understand the fact that this substance, containing six phenyl radicles, can act as if it had the constitution of triphenylmethyl; for if it be assumed that the molecule is decomposed by halogens in such a way that the single bond between the quinonoid nucleus and the adjacent carbon atom is loosened, then we should have two "triphenylmethyl" radicles set free which would at once react with halogen atoms giving two molecules of triphenylmethyl halide.

The quinonoid formula also makes clear the meaning of the experiments of Gomberg and Cone[1] to which we made reference in a previous section. Let us take for example the case of tri-*p*-bromo-triphenylmethyl chloride—



It is clear that, when it is converted into triphenylmethyl by the action of metals, one of the phenyl radicles must become quinonoid; and an examination of the formula of the substance which would be formed if the quinonoid view be correct will show that one of the halogen atoms (marked with an asterisk) should possess the properties of a halogen atom attached to an aliphatic chain rather than those which are shown by halogen atoms bound to aromatic nuclei—



Now, such a halogen atom will be more easily attacked by metals than will be the case with the other bromine atoms in the compound in question; so that we should expect that the action of an excess of, say, silver upon the tri-*p*-bromo-triphenylmethane chloride will result in two reactions, the first of which will lead to the elimination of two chlorine atoms, giving rise to the compound whose formula is shown above, while the further action of the silver will remove two bromine atoms from two molecules of this body, the result being the formation of a substance having the constitution shown below—

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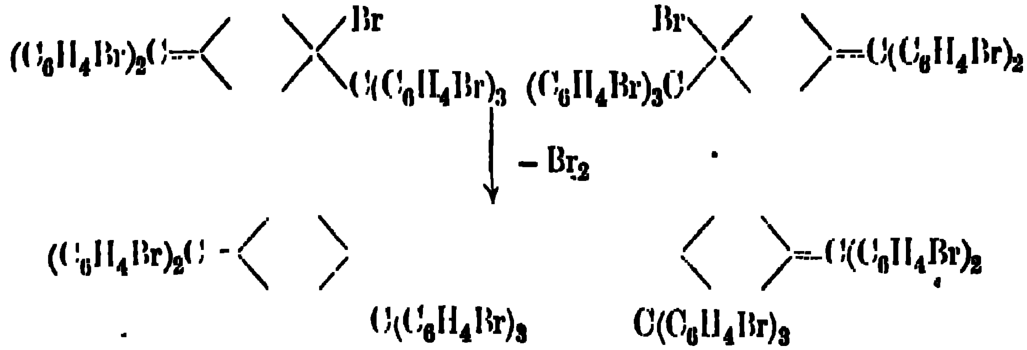
[1] Gomberg and Cone, *Ber.*, 1906, 39, 3274.



The results obtained experimentally by Gomberg and Cone proved that one of the phenyl radicles did actually change from the benzenoid to the quinonoid form; but in the view of these experimenters the assumption of this change alone was not sufficient to account fully for the problems which the properties of triphenylmethyl suggest.

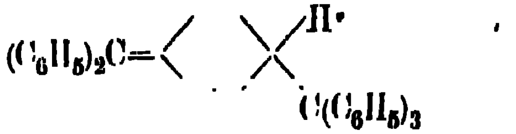
We must now turn to examine the objections which have been brought against the quinonoid view.

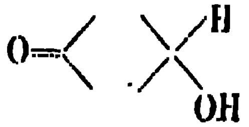
Tschitschibabin[1] pointed out that one of the most speedy and apparently simple reactions which the triphenylmethyl derivatives undergo is the formation of the peroxide—

$$(C_6H_5)_3C—O—O—C(C_6H_5)_3$$

but that if we are to explain this according to the Jacobson formula we should have to assume an extremely complicated isomeric change as the first step in the process.

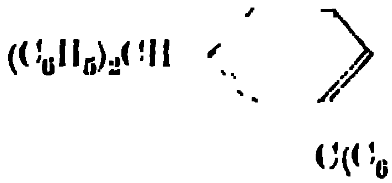
Gomberg and Cone[2] drew attention to the fact that Jacobson makes triphenylmethyl a derivative of a substance analogous to a secondary quinole—

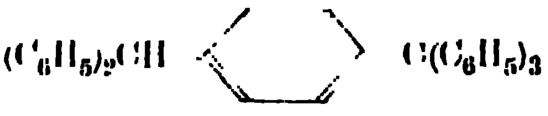




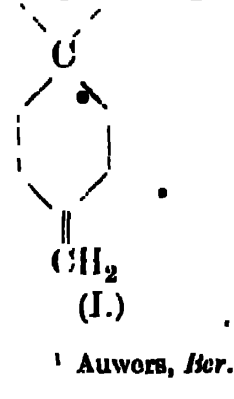
Tschitschibabin, *Ber.*, 1905, **38**, 771.
Gomberg and Cone, *Ber.*, 1906, **38**, 771.

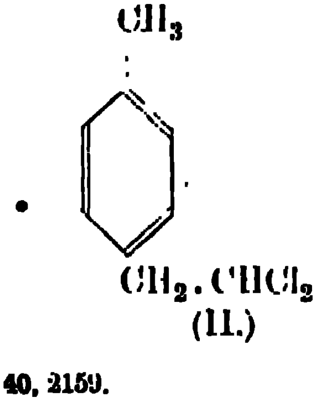
But since secondary quinoles have not yet been proved to be capable of existence, these authors considered doubtful the existence of compounds of the Jacobson type. Furthermore, if we grant the possibility of their existence, it is probable that they will behave like ordinary quinoles, and hence their reactions with acids should resemble to some extent the rearrangements which quinoles undergo under the same conditions. Now in the quinoles, the alkyl group usually wanders to the ortho-position; whence by analogy the substance produced by the action of acids upon triphenylmethyl (Ullmann and Borsum's hydrocarbon) should be represented by the formula (I.) and not by (II.), though Tschitschibabin believed that (II.) was formed. These arguments, as the authors themselves admit, are purely theoretical, and depend largely upon negative evidence.


(I.)


(II.)

From a somewhat similar standpoint Auwers[1] has criticized the Jacobson formula. He points out that the para-methylene quinonoid derivatives show such a tendency to revert to the benzenoid structure that in some cases a profound intramolecular change may take place. For example, in the compound (I.) below, the group $-CHCl_2$ wanders from its original position to the atom next the para-carbon atom in order to facilitate the formation of the benzenoid ring (II.) in preference to the quinonoid one--


(I.)


(II.)

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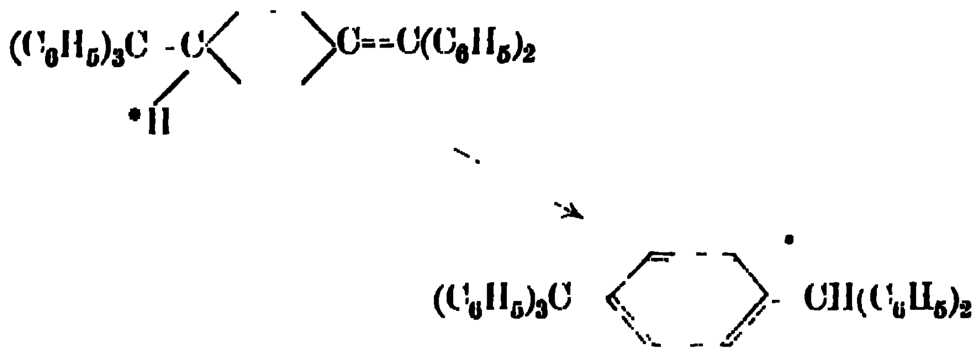
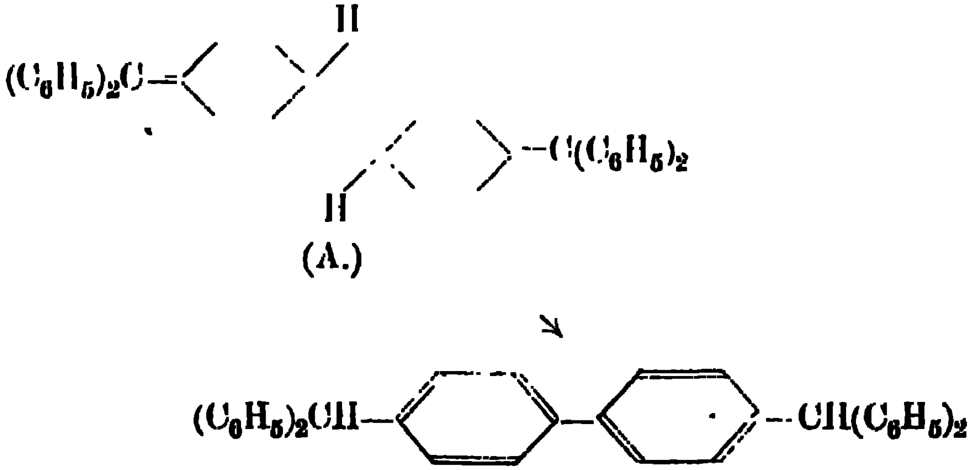
[1] Auwers, *Ber.*, 1907, 40, 2159.

By analogy, it seems hardly likely that the hydrogen atom marked with an asterisk in the Jacobson formula would remain fixed in its present position when, by a similar wandering to the para-carbon atom, it could allow the compound to revert to the benzenoid type—



That such a wandering must be possible is shown by the conversion of the Jacobson compound into that of Ullmann and Borsum by the action of acids; but it seems strange that a compound of the Jacobson formula should exist in the free state at all.

Against the Heintschel formula (A), it has been alleged by Tschitschibabin[1] that it should be easily isomerized into a compound having the structure (B); whereas in practice no such change takes place—



(A.)

(B.)

From the foregoing summary it will be seen that the arguments both in favour of and against the quinonoid structure for triphenylmethyl are based very largely upon considerations of what a compound "ought" to do if it has a structure analogous to some other compound, the latter body being as yet undiscovered in practice. As far as the relevant evidence is concerned, it certainly goes to show that the quinonoid formula is a step in advance of either the triphenylmethyl hypothesis or the hexaphenyl-ethane view, though it fails to account for the molecular weights established by Schlenk.

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[1] Tschitschibabin, *Ber.*, 1905, 38, 771.

5. *The Tautomerism Hypothesis.*

We have now exhausted the possibilities of static formulæ to explain the behaviour of triphenylmethyl; and it is evident that the results have not been completely satisfactory. All the three views which we have discussed in the foregoing sections have certain advantages; and each has its own drawbacks. It thus becomes clear that, if we are to make any further progress towards a solution of the problem, we must contrive some means of uniting the advantages of the various formulæ; while at the same time we must endeavour to minimize their weak points. In order to do this it is obvious that we must turn to modern dynamic ideas and represent triphenylmethyl as a series of equilibrium mixtures of isomerides. Gomberg[1] has developed this line of thought; and if his results do not represent the truth, it seems probable that they come very close to it.

Gomberg's later views took their rise in the fact that there are two varieties of triphenylmethyl which differ from each other in colour: the solid form of the substance is colourless; but in solution this is changed into a yellow compound. Schmidlin[2] states that he has obtained the two forms of the substance in solution. Now, Gomberg assumes in the first place that there are two tautomeric forms of triphenylmethyl, $C_{38}H_{30}$; and in the second place that the radicle triphenylmethyl, $(C_6H_5)_3C$, can exist as such and is also capable of tautomerization. Let us now take up the possible constitution of the solid, colourless modification. This we may suppose to be hexaphenylethane. It is evident that we may assume tautomeric change in this compound, leading us to the following structure:—

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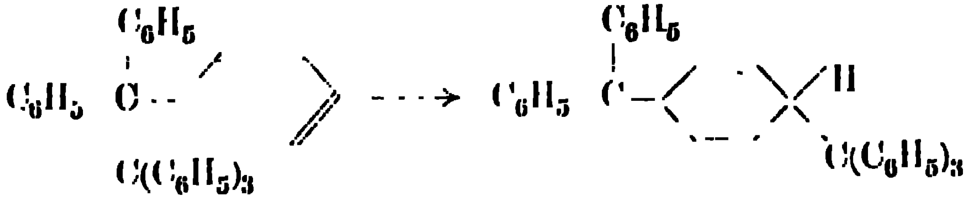
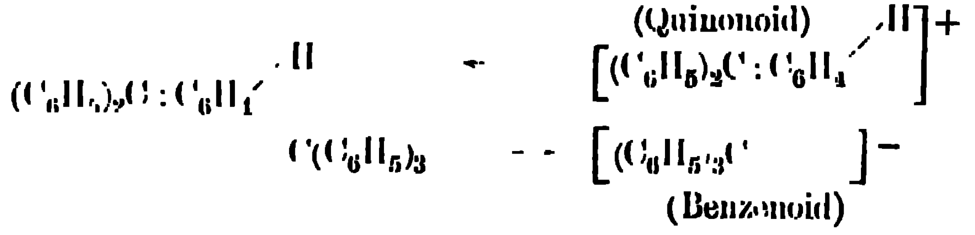
[1] Gomberg, *Ber.*, 1907, 40, 1880.

[2] Schmidlin, *Ber.*, 1908, 41, 2471.



This alteration of the benzenoid into the quinonoid form would be accompanied by a change of the substance from colourless to yellow; and since all ordinary solvents seem to be capable of yielding yellow solutions of triphenylmethyl, we may assume that this change from the benzenoid to the quinonoid form takes place under the action of most solvents during the process of solution.

We must now go a step further and deal with the behaviour of triphenylmethyl dissolved in a medium of high dissociating power, liquid sulphur dioxide. It has been proved by Walden[1] that a solution of the hydrocarbon in this solvent possesses a fairly high conductivity, and that the molecular conductivity increases with the dilution; in other words, the substance behaves just like an ordinary ionized salt. From this behaviour Gomberg deduces that tautomerization is not the only change which triphenylmethyl undergoes as it is dissolved; but that in addition it is dissociated[2] into two ions which we may represent as below. The anion is supposed to have the benzenoid structure, while the kation is quinonoid—



On this view the action of iodine upon triphenylmethyl solutions is explicable. The iodine in solution is supposed to interact with both the anion and the kation, yielding one molecule of benzenoid triphenylmethyl iodide and one molecule in the quinonoid form; but since the latter seems to be incapable of existence in the free state, it is assumed that it undergoes intramolecular change at once and produces a benzenoid molecule. When we turn to the action of oxygen upon triphenylmethyl in solution, however, we have a somewhat different state of affairs, since only the anion unites with oxygen. (This follows from the fact that the peroxide formed has the benzenoid structure, whereas the action of oxygen upon the quinonoid ion would give rise to a highly complicated product which is not observed among the reaction products.) We are thus led to the further assumption that in the process of peroxide formation the first step is the oxidation of the benzenoid ions; as these are removed from the solution, equilibrium is disturbed; and, in order to re-establish it, some of the quinonoid ions must re-tautomerize into the benzenoid form. They in turn are removed by the oxygen; and the process continues until all the triphenylmethyl is exhausted.

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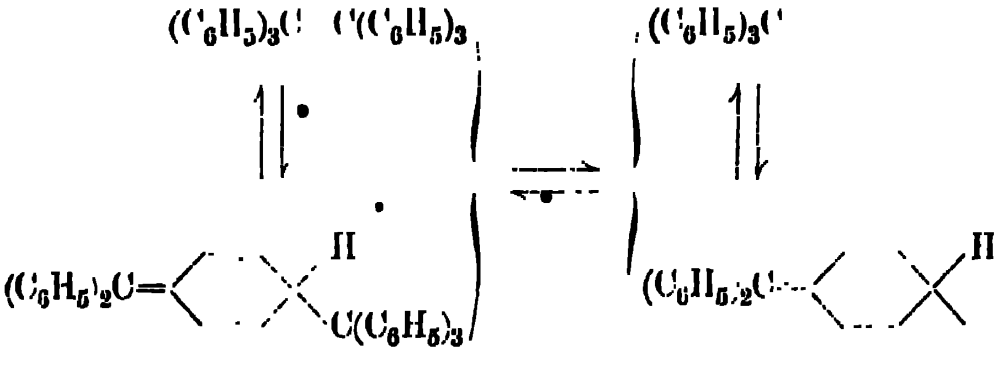
[1] Walden, *Zeit. phys. Chem.*, 1903, 43, 443; Gomberg and Cone, *Ber.*, 1904, 37, 2403.

[2] Compare Dq *Trans.*, 1919, 115, 127.

The same tautomerization process can be invoked to explain why triphenylmethyl gives a yellow solution with ethers, esters, and ketones, while the solid double compounds which crystallize out from these solutions are colourless. In this case the benzenoid ions may be assumed to unite with the quadrivalent oxygen of the ethers, etc.; and in order to take their place some of the quinonoid ions are converted into benzenoid ones.

According to Gomberg,[1] then, we can explain all the important properties of triphenylmethyl on the basis of the following hypothesis: (1) tautomerization of hexaphenylethane to a quinonoid substance having the Jacobson formula; (2) partial dissociation of this compound into positive and negative ions in all solvents; (3) mutual interconvertibility of these ions by tautomeric change; and (4) the existence of trivalent carbon atoms giving rise to free radicles. Thus a complete representation of triphenylmethyl's mutations is given by the following scheme:—



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[1] Gomberg and Schoepfle, *J. Amer. Chem. Soc.*, 1917, **39**, 1652.

One final piece of evidence may be mentioned here, though its bearing upon the triphenylmethyl problem is an indirect one. If we discard the hypothesis of a quinonoid structure in triphenylmethyl, we are driven back to the idea that the three phenyl radicles, in view of their great amount of residual affinity, affect the fourth valency of the methyl carbon atom and thus allow its trivalence. But if this were so, then three other unsaturated radicles should have the same effect. Now tetranitromethane in certain solvents[1] shows a development of colour similar to that exhibited by triphenylmethyl; and it might be assumed that under these circumstances it was dissociated into a free nitro-group and trinitromethyl:—

$$(NO_2)_3C.NO_2 \dashrightarrow (NO_2)_3C— \quad + \quad —NO_2$$

The fact that the absorption band produced is independent of the nature of the solvent used[2] (provided that any colour is developed at all) seems to support this view.

To test this idea, a series of determinations of the molecular weight of tetranitromethane was carried out[3] in solvents yielding coloured solutions with the solute and also others in which no colour was developed. The method employed was the cryoscopic one. In no case was any sign of dissociation to be found. Solutions of tetranitromethane in acetic acid (where no colour is exhibited) and in napthalene (which changes to the tint of azobenzene in presence of 2 per cent. of tetranitromethane) gave freezing-point depressions agreeing with the molecular weight of tetranitromethane within 0·2 per cent. Evidently no dissociation occurs in this case, although the three nitro-groups are quite as "negative" and unsaturated as the three phenyl radicles of triphenylmethane are. This seems to show that the explanation of the behaviour of triphenylmethyl must be sought in the nature of the phenyl radicles as distinct from their mere residual affinity.

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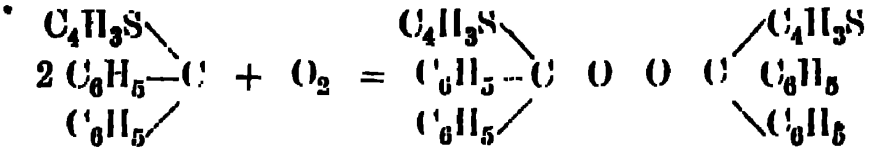
[1] Ostromisslensky, *J. pr. Chem.*, 1911, **84**, 489; Clarke, Macbeth, and Stewart, *Proc.*, 1913, **29**, 161.

[2] Harper and Macbeth, *Trans.*, 1915, **107**, 87; Macbeth, *ibid.*, 1824.

[3] Stewart, unpublished observation.

6. *Thiophene Analogues of Triphenylmethyl.*

Gomberg and Jickling[1] have extended the study of free radicles into the region of the heterocyclic compounds. From α-iodothiophene and benzophenone they prepared, by the Grignard reaction, thienyl-diphenyl carbinol; from which, by the action of hydrogen chloride, they obtained the corresponding chloride. When the last substance is treated in benzene solution with molecular silver or other metals, it exhibits a deep red colour and absorbs oxygen freely. The amount of oxygen absorbed indicates that the following reaction probably takes place:—



$$2\,\begin{array}{l}C_4H_3S\diagdown\\C_6H_5{-}C\\C_6H_5\diagup\end{array} + O_2 = \begin{array}{l}C_4H_3S\diagdown\\C_6H_5{-}C\;\;O\;\;O\;\;C\;\;C_6H_5\\C_6H_5\diagup\end{array}\begin{array}{l}\diagup C_4H_3S\\ \\ \diagdown C_6H_5\end{array}$$

thus bringing the new compound into line with triphenylmethyl in peroxide formation.

This opens up prospects of considerable interest; for the production or non-production of a trithienylmethyl would throw light upon the constitution of triphenylmethyl itself.

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[1] Gomberg and Jickling, *J. Amer. Chem. Soc.*, 1913, **35**, 446.

CHAPTER XII

OTHER ELEMENTS WHICH EXHIBIT ABNORMAL VALENCY

A. Introductory

In view of the interest excited by the triphenylmethyl problem from 1900 onwards, it seems strange that no one at that time appears to have thought of examining other compounds which show some structural analogy with hexaphenyl-ethane.

$$(C_6H_5)_3C.C(C_6H_5)_3 \quad (C_6H_5)_2N.N(C_6H_5)_2 \quad C_6H_5.O.O.C_6H_5$$
$$(C_6H_5)_3Pb.Pb(C_6H_5)_3 \quad (C_6H_5)_2As.As(C_6H_5)_2 \quad C_6H_5.S.S.C_6H_5$$

In each of the formulæ shown above there is a symmetrical structure; all the formulæ contain a central single bond in the molecule; and the various substances represent the highest possible phenyl-substitution product of their type.

A compound has now been isolated which from certain of its reactions, appears to contain trivalent lead, though it differs to some extent from the carbon analogue, triphenylmethyl.

Tetraphenylhydrazine was already known at the time when triphenylmethyl was arousing interest by its peculiar nature; yet no one seems to have been struck by the analogy between it and hexaphenyl-ethane; and it was quite accidentally, in 1906, that the close correspondence between the two series was first brought out in practice. It has since been shown that, just as the free radicle triphenylmethyl can exist in solution, so can the corresponding diphenylhydrazyl grouping $(C_6H_5)_2N$ appear in the free state; and if carbon is to be considered as a trivalent element in certain circumstances, we cannot deny the possibility of divalent nitrogen derivatives. Between the two series a strong resemblance undoubtedly exists, though the bond N—N is much less readily ruptured than is the case with the single linkage between the central carbon atoms of Gomberg's hydrocarbon.

With regard to the analogous phenyl derivatives of the divalent elements, it is found that experimental evidence points to the possibility of aryl peroxides yielding dissociation products;[1] whilst apparently diphenyl disulphide can, under certain circumstances, give rise to a free radicle. There are indications that derivatives of monovalent mercury may be capable of existence. In the following sections of this chapter the behaviour of these compounds will be briefly surveyed.

B. TRIVALENT LEAD

When to an ethereal solution of magnesium *p*-2-xylyl bromide we add finely-powdered lead dichloride in the proportion required by the equation:—

$$3\,PbCl_2 + 6Br.Mg.C_8H_9 = 2Pb(C_8H_9)_3 + Pb + 3\,MgCl_2 + 3\,MgBr_2$$

a greenish-yellow crystalline material can be isolated from the reaction-mixture.[2] The molecular weight of the substance, determined by the cryoscopic method in benzene solution, corresponds to the formula $(C_8H_9)_3Pb \cdot Pb(C_8H_9)_3$; and the body appears to be the lead analogue of hexaphenyl-ethane.

It does not oxidize in air under ordinary conditions, wherein it differs from its carbon analogue; but with bromine it yields $Br \cdot Pb(C_8H_9)_3$, just as triphenylmethyl gives triphenyl-bromomethane.

The lead derivative is quite stable up to a temperature of 220°; but in solution it appears to be remarkably photosensitive, being readily decomposed by the action of light. By the Grignard reaction, it yields lead tetra-*p*-2-xylyl, which is only decomposed at temperatures above 270.°

Attempts to prepare the corresponding simpler derivatives (such as lead triphenyl) by the same method have not been successful, the tetra-aryl compounds being obtained instead.

C. DIVALENT AND QUADRIVALENT NITROGEN

1. *The Tetra-aryl-hydrazines and their Reactions.*

Tetraphenyl-hydrazine can be prepared either by the action of iodine upon the sodium derivative of diphenylamine[3] or by the oxidation of diphenylamine in an organic solvent by means of lead oxide or potassium permanganate.[1] Obtained by any of these methods, it is a colourless solid melting at 144° C.

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[1] Pummerer and Cherbuliez, *Ber.*, 1914, 47, 2957.

[2] Krause and Schmitz, *Ber.*, 1919, 52 (B), 2165.

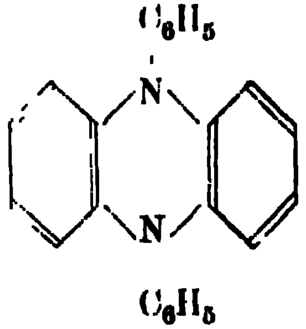
[3] Chattaway and Ingle, *Trans.*, 1895, 67, 1090.

As a class the tetra-aryl-hydrazines are stable substances when in the solid state, though they are easily affected by light and are rapidly changed when dissolved in various solvents. Nascent hydrogen converts them with ease into two molecules of the diarylamine from which they were originally produced.

Their most peculiar behaviour is observed when they are treated with acid. In their ordinary form they possess no basic properties; for anhydrous mineral acids give no normal (colourless) salts. On the other hand, when they are acted on by acids, even in organic solvents, they exhibit intense colours,* green, blue, or violet.[2] The coloured derivatives can be isolated in an impure condition; and when they are treated with alkali they regenerate the parent hydrazines. They must therefore be regarded as salt-like addition products of the undecomposed hydrazines.[3]

These coloured products are extremely labile and soon decompose under ordinary conditions, yielding a mixture of several different compounds.[4] Thus in presence of acids, tetraphenyl-hydrazine gives diphenylamine, *p*-chloro-anilido-triphenylamine (I.), diphenylbenzidine (II.), and a perazine-derivative (III.)—

$Cl.C_6H_4.NH.C_6H_4.N(C_6H_5)_2$ (I.) $C_6H_5.NH.C_6H_4.C_6H_4.NH.C_6H_5$ (II.)



(III.)

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[1] Wieland and Gambarjan, *Ber.*, 1906, 39, 1499.

* Similar colours are obtained with halogens, thionyl chloride, ferric chloride, aluminium chloride, zinc chloride, and the pentachlorides of phosphorus and antimony.

[2] *Ibid.*

[3] Wieland, *Die Hydrazine*, 1913, p. 63.

[4] Wieland, *Annalen*, 1911, 381, 200; 1912, 392, 169; *Ber.*, 1907, 40, 4262; 1908, 41, 3478.

The presence of acids is not essential to ensure the breakdown of the tetra-aryl-hydrazines; for with some of them it is only necessary to heat the substance itself in benzene or toluene solution, whereupon decomposition takes place and follows a course similar to that traced when acids are present, though naturally, with slight variations due to the absence of acidic radicles.[1]

The influence of solvents upon the hydrazines manifests itself in another manner. As has been mentioned, the hydrazines are colourless in the solid state; but when they are dissolved in organic solvents and then heated, a marked colour makes its appearance,[*] which disappears again if the substance be cooled immediately. Colours also make their appearance when the hydrazines are bombarded with cathode rays and kept cool with liquid air.[2] As soon as the bombardment ceases, the substance reverts to its original colourless condition.[†]

When treated with nitrogen peroxide in toluene solution at 90° C., tetraphenyl-hydrazine reacts and produces nitroso-diphenylamine (I.); whilst with triphenylmethyl it yields triphenylmethyl-diphenylamine[‡] (II.)—

$$(C_6H_5)_2N \quad N:O \qquad\qquad (C_6H_5)_3C \quad N(C_6H_5)_2$$

(I.) (II.)

Alkali metals act on the tetra-aryl-hydrazine with greater or less readiness, producing compounds of the type $R_2:N.Na$, the reaction being similar to that observed in the case of triphenylmethyl.[3]

In conclusion, it must be pointed out that in one case at least the general synthetic method for preparing tetra-aryl-hydrazines breaks down. When carbazole—

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[1] Wieland and Lecher, *Ber.*, 1912, **45**, 2600.

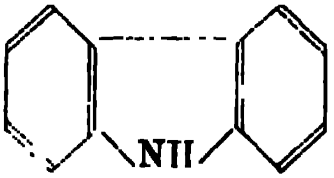
[*] Cryoscopic molecular weight determinations prove that the substance $[(CH_3)_2N.C_6H_4]_2N.N[C_6H_4N(CH_3)_2]_2$ is dissociated to an extent of 10 per cent. in benzene solution and 21 per cent. in a solution of nitrobenzene (Wieland, *Ber.*, 1915, **48**, 1078).

[2] Wieland, *Annalen*, 1911, **381**, 200.

[†] Exactly similar results are obtained with triphenylmethyl derivatives (Schlenk and Herzenstein, *Annalen*, 1910, **372**, 1).

[‡] Exactly similar results are obtained with triphenylmethyl derivatives (Schlenk and Herzenstein, *Annalen*, 1910, **372**, 1).

[3] Schlenk and Marcus, *Ber.*, 1914, **47**, 1664.



is oxidized with the usual reagents, it does not behave like diphenylamine,[1] though it contains the diphenylamine skeleton. Apparently the presence of the pyrrol ring in the compound has some influence upon the reaction; and it is suggested that the extra valency of the nitrogen atom is in this case absorbed by that portion of the molecule.

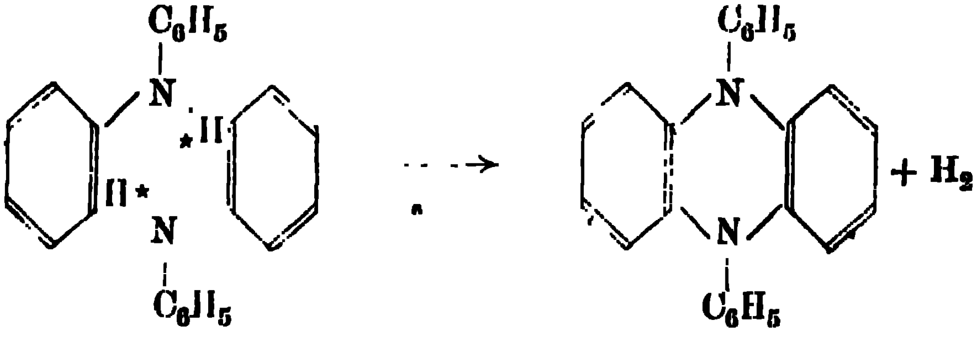
2. *Wieland's Hypothesis of Divalent Nitrogen.*

In order to explain the reactions described in the foregoing section, Wieland[2] proposes to regard the tetra-alkly-hydrazines as analogues of the triphenylmethyl series; so that under certain conditions he assumes a depolymerization of the substituted hydrazine which parallels the formation of triphenylmethyl from hexaphenyl-ethane—

$$(C_6H_5)_2N-N(C_6H_5)_2 \longrightarrow 2\,(C_6H_5)_2N$$
$$(C_6H_5)_3-C-C=(C_6H_5) \longrightarrow 2\,C(C_6H_5)_3$$

The colours observed when tetraphenyl-hydrazine derivatives are treated with acids or with reagents such as stannic chloride are thus brought into line with those which are obtained in the triphenylcarbinol series under similar conditions.

The formation of a dihydrophenazine derivative and diphenylamine is explained by the mutual oxidation and reduction of four free radicles in the following manner. In the first place, two of them unite with the elimination of two hydrogen atoms (marked with an asterisk) to form diphenyl-dihydrophenazine—



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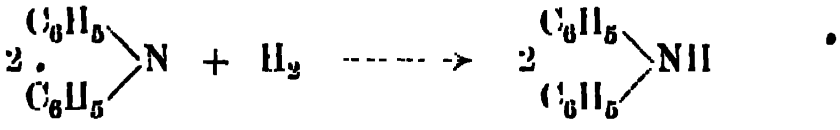
[1] Wieland and Gambarjan, *Ber.*, 1906, **39**, 1499.

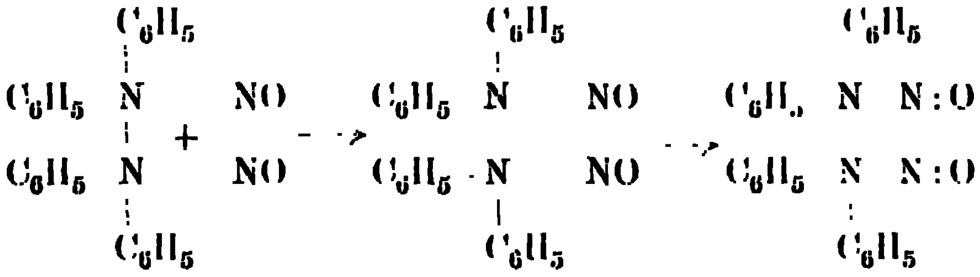
[2] Wieland, *Annalen*, 1911, **381**, 200; 1912, **392**, 127; 193. **401**, 233.

These two hydrogen atoms, thus set free, then reduce the two other free radicles to form two molecules of diphenylamine—



$$2\cdot\begin{matrix}C_6H_5\\C_6H_5\end{matrix}\!\!>N + H_2 \dashrightarrow 2\begin{matrix}C_6H_5\\C_6H_5\end{matrix}\!\!>NH$$

The production of nitroso-diphenylamine, on this hypothesis, may be represented thus—

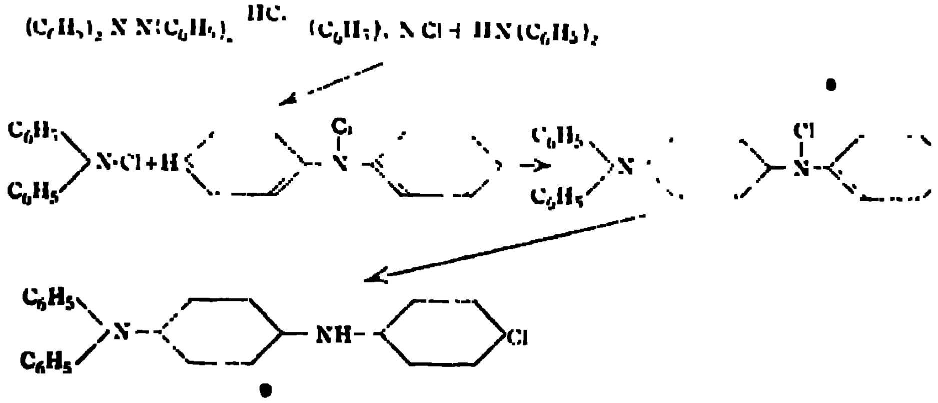


$$\begin{array}{cccccccccccc} & C_6H_5 & & & & & C_6H_5 & & & & C_6H_5 & \\ & \vdots & & & & & | & & & & & \\ C_6H_5 & N & & NO & & C_6H_5 & N & NO & & C_6H_5 & N & N:O \\ & \vdots & + & & \dashrightarrow & & & & \dashrightarrow & & & \\ C_6H_5 & N & & NO & & C_6H_5 & -N & NO & & C_6H_5 & N & N:O \\ & \vdots & & & & & | & & & & \vdots & \\ & C_6H_5 & & & & & C_6H_5 & & & & C_6H_5 & \end{array}$$

and the reaction with triphenylmethyl is simply a union of the two free radicles to form triphenylmethyl-diphenylamine—

$$(C_6H_5)_3C + N(C_6H_5)_2 \dashrightarrow (C_6H_5)_3 \cdot N(C_6H_5)_2$$

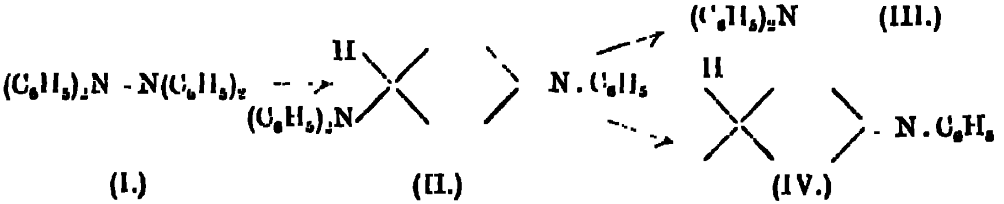
To account for the formation of *p*-chloro-anilido-triphenylamine, Wieland assumes that the first action of acids upon tetraphenyl-hydrazine is to decompose it into one molecule of diphenylamine and one molecule of chloro-diphenylamine, two molecules of which then interact as shown below—



3. *Stewart's Application of the Quinonoid Hypothesis.*

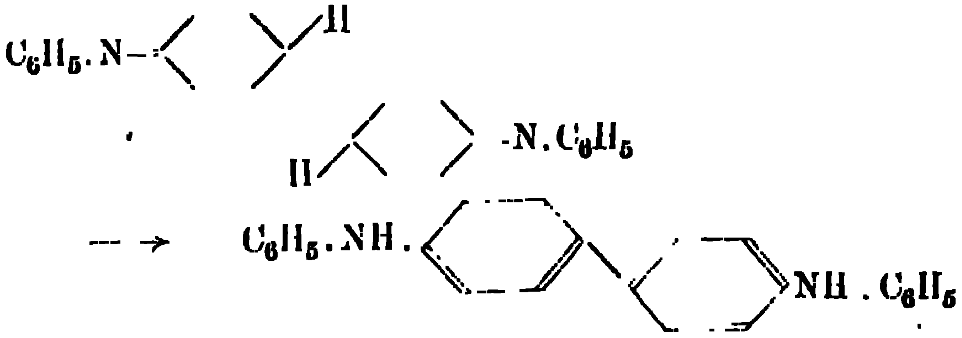
The parallelism between the tetraphenyl-hydrazine derivatives and the triphenylmethyl group is so close that it seems not unwarrantable to extend to the former the ideas which have been used to account for the behaviour of the trivalent carbon compounds.

In the triphenylmethyl group, it was assumed that hexaphenyl-ethane was capable of intramolecular change resulting in a quinonoid structure. An analogous change in tetraphenyl-hydrazine would result in the formation of a compound of the type (II.) which, if we follow out the parallel, would dissociate into a benzenoid portion (III.) and a quinonoid part (IV.)



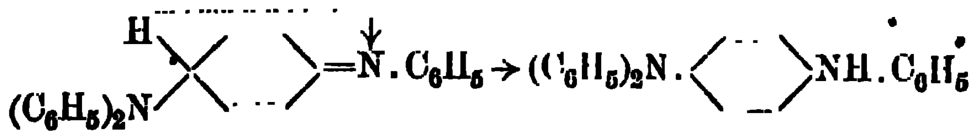
The presence of the quinonoid structure here would account for the appearance of colour when colourless tetraphenylhydrazine is heated in solution, and also for the readiness with which the substance is affected by light.

To account for the production of diphenylbenzidine from the hydrazine, it is only necessary to assume that two molecules of (IV.) join together and then rearrange themselves into the benzenoid form—



To explain the production of *p*-chloro-anilido-triphenylamine, it may be assumed that in acid solution the radicle $(C_6H_5)_2N$ is attacked by a chlorine ion, giving chloro-diphenylamine, after which the reactions would take place according to Wieland's suggestion. The occurrence of the parent substance, anilido-triphenylamine, which is noticed when tetraphenyl-hydrazine is heated in benzene solution, can be even more simply explained by a wandering of a hydrogen atom;

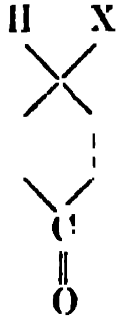
thus recalling the formation of Ullmann and Borsum's hydrocarbon in the case of triphenylmethyl—



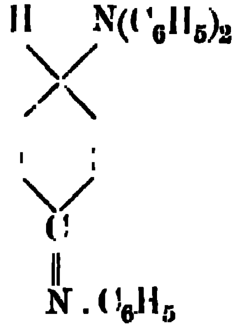
Anilido-triphenylamine.

The interaction with triphenylmethyl and with nitrogen peroxide is easily accounted for by assuming that these two reagents combine directly with the free benzenoid radicles (III.).

In order to make clear the formation of the perazine derivative it must be pointed out that along with one molecule of this substance, the reaction gives rise simultaneously to two molecules of diphenylamine. Now an examination of the quinonoid structure proposed for tetraphenyl-hydrazine suggests a resemblance to the quinole constitution—

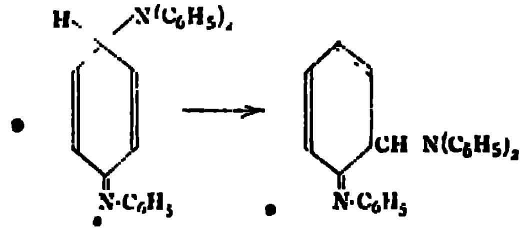


Quinole.

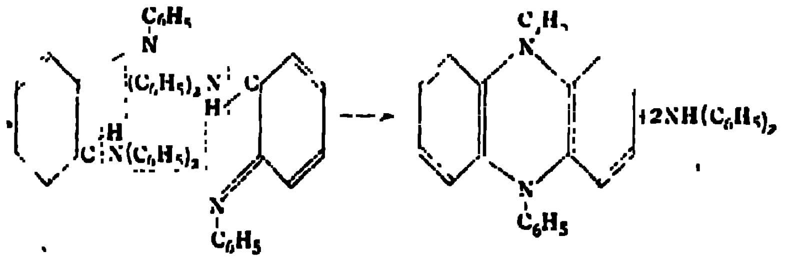


Tetraphenyl-hydrazine.

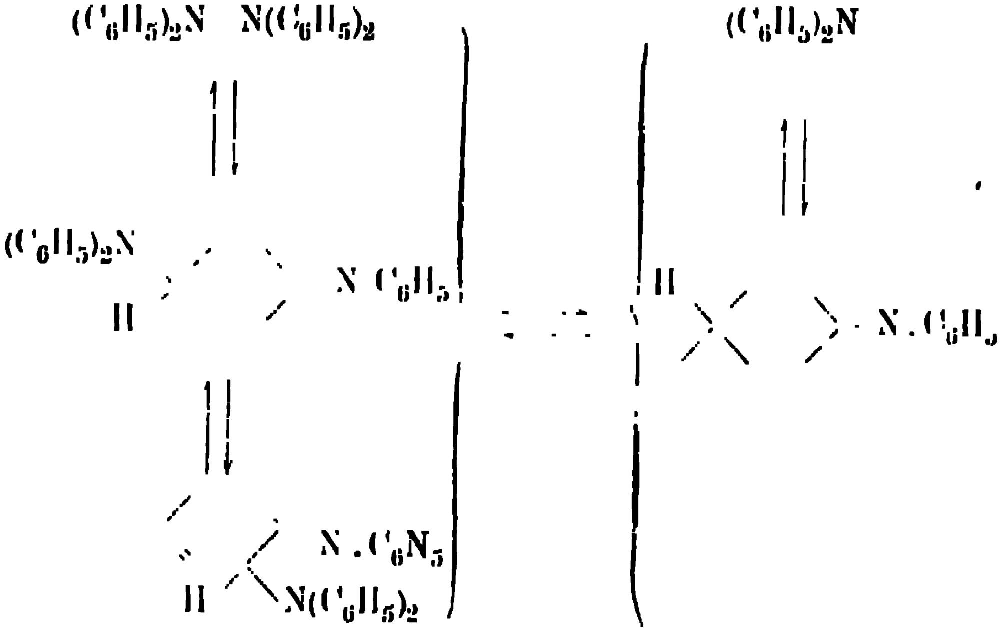
and just as some quinoles exhibit a wandering of the group X to the nucleus, so we may assume a similar wandering to take place in the case of tetraphenyl-hydrazine, giving rise to a compound of the following structure—



Two molecules of this would combine directly to produce a perazine and at the same time eliminate two molecules of diphenylamine (as shown by the dotted line) for each molecule of perazine produced—



Thus in order to account satisfactorily for the various reactions of tetraphenyl-hydrazine, it is necessary to assume the following series of equilibria:—



4. *A Derivative containing Quadrivalent Nitrogen.*

The oxidation of diphenyl-hydroxylamine with silver hydroxide yields a compound[1] which appears to have the formula shown below—

$$(C_6H_5)_2:N.OH \xrightarrow{Ag_2O} (C_6H_5)_2:N:O$$

Owing to its analogy in structure with nitrogen peroxide, this substance is termed diphenyl-nitrogen oxide. It is a crystalline compound, deep red in tint; and its vapour resembles that of nitrogen peroxide. It liberates iodine from potassium iodide -

$$(C_6H_5)_2:N:O + 2HI = (C_6H_5)_2:NH + 2I + H_2O$$

---

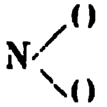
[1] Wieland and Offenbächer, *Ber.*, 1914, 46, 2111.

With bromine it gives a halogen derivative of diphenylamine containing two bromine atoms attached to one phenyl nucleus and one bromine atom in the other. With nitrogen peroxide and triphenylmethyl it reacts readily. Concentrated mineral acids react with almost explosive violence upon the new compound.

The molecular weight determined cryoscopically in benzene corresponds to the monomolecular formula; and this apparently remains unaltered even in a mixture of ether and carbon dioxide, for at – 60° C. the substance can be recrystallized from ether and still retain its red colour.

One point of interest in connection with the compound is that its discovery throws considerable doubt upon a structure suggested for nitrogen peroxide: for it is clear that diphenylnitrogen oxide resembles nitrogen oxide closely; and this tends to support the formula (II.) as against (III.)

$$(C_6H_5)_2\quad N\quad O \qquad\qquad O\ {-}N{-}\ O$$



(I) (II.) (III.)

The formation of $Br_3C_6H_2{-}NH{-}C_6H_4Br$ by the action of bromine upon the substance may point to the existence of a quinonoid grouping in the molecule; and it is possible that the case may be one of trivalent carbon instead of an example of quadrivalent nitrogen. Too little is known of the subject at present to make it worth while to speculate further.

D. DERIVATIVES OF MONOVALENT SULPHUR.

The oxidation of phenyl mercaptan yields phenyl disulphide,

$$C_6H_5\quad S\quad S\quad C_6H_5$$

This substance in the solid state is colourless, but when it is dissolved in any indifferent solvent, the solution shows a faint yellow tinge, and the colour is intensified by raising the temperature. On cooling, the solution regains its original tint. This change in colour cannot be attributed to dissociation, according to Lecher,[1] since the solutions do not deviate from Beer's Law when examined in a colorimeter; so that the case is not parallel to that of triphenylmethyl in this respect.

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[1] Lecher, *Ber.*, 1915, 48, 524.

Further, in the case of *p*-dimethylanilido-disulphide—

$$(CH_3)_2N-C_6H_4-S-S-C_6H_4-N(CH_3)_2$$

an analogous colour change is observed when the solid substance is heated and cooled.

To explain these phenomena, Lecher suggests that the bond between the sulphur atoms is not broken but is merely weakened; and that the weakening of the valency and the development of colour are parallel changes.

Evidence of this weakening of the bond between the sulphur atoms was sought for in various reactions. For example, at ordinary temperatures or even at 80° C. sodium has little effect upon phenyl disulphide; but at 125° C. it reacts to produce sodium mercaptide—

$$C_6H_5-S-S-C_6H_5 + 2Na = 2C_6H_5-S-Na$$

The weakness of the bond between the sulphur atoms is also indicated by the interaction of *p*-dimethylanilido-disulphide and triphenylmethyl, which gives rise to 1-dimethylamido-phenyl-4-triphenylmethyl disulphide—

$$(CH_3)_2N.C_6H_4-S-S-C_6H_4.N(CH_3)_2 + 2(C_6H_5)_3C$$
$$= 2(CH_3)_2N.C_6H_4.S.C(C_6H_5)_3$$

These reactions suggest that under certain conditions it might be possible to obtain derivatives of monovalent sulphur; and though no actual isolation of such compounds has yet been achieved, their existence has been rendered probable by the following evidence.[1] Phenyl-triphenylmethyl sulphide can be obtained by the action of triphenyl-chloro-methane upon sodium phenyl mercaptide—

$$C_6H_5.S.Na + Cl.C(C_6H_5)_3 = C_6H_5.S.C(C_6H_5)_3 + NaCl$$

Now this sulphide becomes strongly yellow when heated in ethyl benzoate solution; and an examination of the spectrum proves that triphenylmethyl is present. By shaking the solution in the air, the triphenylmethyl is oxidized, the solution becomes colourless; and by further shaking in an indifferent atmosphere the yellow colour of triphenylmethyl reappears owing to a further decomposition of sulphide. The only way in which this reaction can reasonably be expressed is as follows:—

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[1] Lecher, *Ber.*, 1915, **48**, 524; 1920, **53**, 577.

$$C_6H_5 \cdot S \quad C(C_6H_5)_3 = C_6H_5 . S + C(C_6H_5)_3$$

Further evidence[1] is found in the examination of mercury phenyl mercaptide, $C_6H_5 . S . Hg . S . C_6H_5$. It was observed by Dreher and Otto,[2] that this body, when heated, breaks up into mercury and phenyl disulphide; and this suggests that heat loosens the bond between the sulphur and mercury atoms. On Lecher's view, the weakening of the valency force ought to be accompanied by a development of colour as the temperature rises. This actually proves to be the case. Whether dry or in solution, the mercaptide is colourless at ordinary temperatures but becomes yellow when heated, though no mercury separates from it under the experimental conditions employed.

Lecher suggests that the Dreher-Otto reaction is a reversible one which may take one of the two following courses:—

$$\begin{array}{lrcl}
\text{(I.)} & (C_6H_5 . S)_2Hg & \rightleftharpoons & C_6H_5S . S . C_6H_5 + Hg \\
\text{(II.)} & (C_6H_5 . S)_2Hg & \rightleftharpoons & 2C_6H_5 . S + Hg \\
 & 2C_6H_5 . S & \rightleftharpoons & C_6H_5 . S . S . C_6H_5
\end{array}$$

If it can be proved that the reaction includes the two equilibria shown in (II.), the existence of monovalent sulphur would be established; but at present the subject is not beyond dispute; and we must wait for further evidence before classing monovalent sulphur compounds along with the better-established cases of trivalent carbon and divalent nitrogen.

E. A DERIVATIVE OF MONOVALENT OXYGEN.

When β-dinaphthol (I.) is oxidized with silver hydroxide, it yields a substance termed hydroxy-naphthylene oxide, to which the formula (II.) is ascribed. By treating this with potassium ferricyanide or indigo white, dehydroxy-dinaphthylene oxide is formed, which is supposed to have the structure (III.) or (III*a*.). This body, when dissolved in various solvents, shows colour phenomena akin to those observed in the triphenylmethyl series; and, partly on this ground, it is assumed to dissociate into radicles[1] which have either of the structures (IV.) and (V.).

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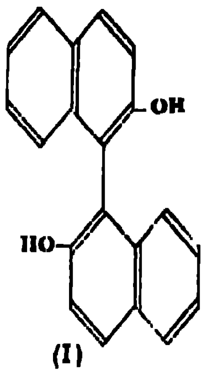
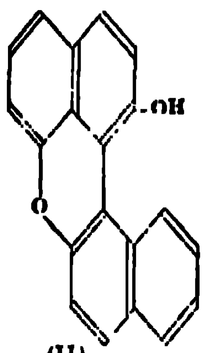
[1] Lecher, *Ber.*, 1915, **48**, 1425; 1920, **53**, 577.

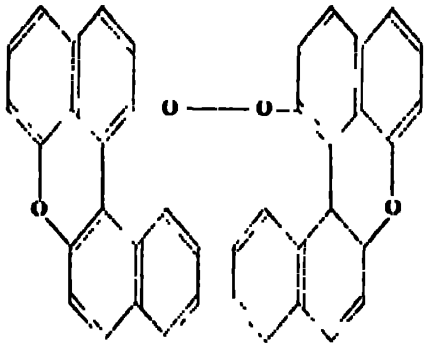
[2] Dreher and Otto, *Annalen*, 1870, **154**, 178.



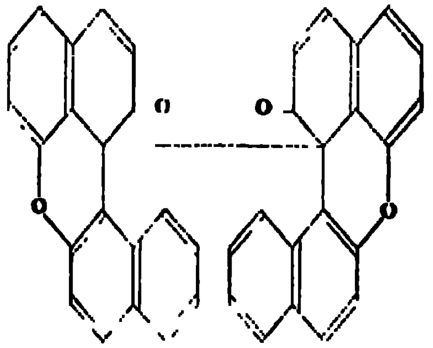
(I)



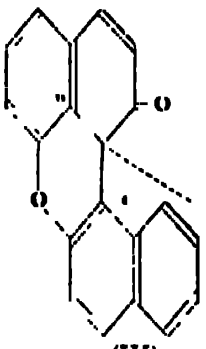
(II)



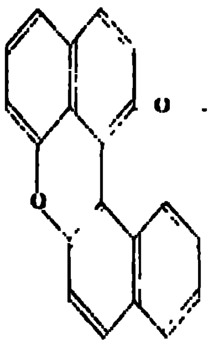
III



IIIa



(IV)



(V)

The supposed free radicle reacts readily with oxygen (though less rapidly than triphenylmethyl) forming an ochreous peroxide. Iodine also acts upon it more slowly than might have been anticipated. Hydrochloric acid decomposes it. Triphenylmethyl, cyclopentadiene, and pinene add themselves on to the radicle. Nitrogen peroxide forms an additive compound in ethereal or benzene solution but does not attack the radicle to any extent in chloroform solution. When the substance is boiled in benzene solution it undergoes decomposition, yielding hydroxy-dinaphthylene oxide and dinaphthylene dioxide.

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[1] Pummerer and Frankfurter, *Ber.*, 1914, 46, 1472; compare Pummerer and Cherbuliez, *ibid.*, 2957.

It will be seen from the above data that the compound is extremely complicated; its reactions have not been fully studied; and it may be well to refrain from laying too much stress upon its structure till its properties have been more thoroughly investigated.

F. MONOVALENT MERCURY.

If a liquid ammonia solution of methyl mercury chloride, $CH_3 . Hg . Cl$, is electrolysed with a small cathode, a highly attenuated opaque mass collects around the cathode.[1] When the mass is collected and allowed to warm up to near ordinary temperature it suddenly undergoes decomposition with the evolution of heat. The reaction appears to correspond to the following equation :—

$$2CH_3 . Hg = Hg + Hg(CH_3)_2$$

Other compounds containing other alkyl radicles and acidic groups behave similarly.

The material is black, like a finely divided metal; and it is a good conductor of electricity. It does not amalgamate with mercury to any marked extent.

It is suggested by Kraus that this compound contains monovalent mercury; and this is possibly the case. On the other hand, it is not improbable that it is actually $CH_3 . Hg . Hg . CH_3$; which might be formed at the small cathode just as persulphates are formed from sulphates under similar conditions at the anode. Further research will probably decide which of these views is correct.

G. CONCLUSION.

The nature and behaviour of the triaryl-methyls and the tetra-aryl-hydrazines suggest problems which bring us to the very bases upon which rest our modern views of structural chemistry. Once the idea of "free radicles" is accepted, our long-tried dogma of the quadrivalence of carbon comes into the scales for a final test. It is doubtful if we shall throw over the older ideas suddenly. Already there is a tendency to look for a new conception of valency, a tendency which is displayed in the modern theories of partial valency and residual affinity: but these views are at present disjointed; and there is little sign of their being welded into a connected whole which will carry conviction by its clarity and flexibility.

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[1] Kraus, *J. Amer. Chem. Soc.*, 1913, **35**, 1732.

In the meantime, it seems desirable that further examples of these peculiar compounds should be examined; so that as wide a basis as possible may be used for generalization. Attempts[1] have been made to prepare analogues of tetraphenyl-hydrazine in the arsenic group, such as

$$(C_6H_5)_2As-As(C_6H_5)_2$$

but, up to the present, no actual proof of the dissociation of such substances into free radicles has been obtained. Possibly the temperature employed was not sufficiently high* to produce a rupture between the arsenic atoms. Further experiments may prove more successful; or fruitful subjects for investigation might be found in the analogous compounds derived from phosphorus, antimony, or bismuth. The analogues of carbon (silicon and tin) also suggest themselves for research purposes; for it can hardly be assumed that carbon, sulphur, lead, and nitrogen are the only atoms capable of showing this peculiarity.

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[1] Schlenk, *Annalen*, 1912, **394**, 216; Porter and Borgstrom, *J. Amer. Chem. Soc.*, 1919. **41**, 2048.

* A solution of the substance in boiling benzene was used.

CHAPTER XIII

MODERN FORMULÆ AND THEIR FAILINGS

An unbiassed survey of the fields covered by organic chemistry cannot fail to reveal to any critical mind the fact that our structural formulæ are becoming less and less able to cope with the strain which modern research is placing upon them. It is true that for work-a-day purposes they still answer admirably; and from the point of view of teaching it is doubtful if anything better could be devised. But when we go into the matter beyond the mere surface, things are not so satisfactory as they may appear to the superficial observer. In the present chapter an attempt will be made to indicate briefly some points in the problem.

In the first place, it will be well to inquire as to the exact nature of our present-day formulæ. According to Kekulé,[1] structural formulæ were "decomposition" formulæ:—

"Rational formulæ are decomposition formulæ, and in the present state of chemical science can be nothing more. These formulæ give us pictures of the chemical nature of substances; because the manner of writing them indicates the atomic groups which remain unattacked in certain reactions. . . . Every formula which expresses definite metamorphoses of a compound is *rational;* that one of the different rational formulæ is the *most rational,* which expresses the greatest number of the metamorphoses."

Couper,[2] on the other hand, put the case as follows:—

"Gerhardt . . . is led to think it necessary to restrict chemical science to the arrangement of bodies according to their decompositions, and to deny the possibility of our comprehending their molecular constitution. Can such a view tend to the advancement of science? Would it not be only rational, in accepting this veto, to renounce chemical research altogether?"

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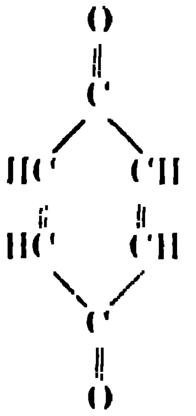
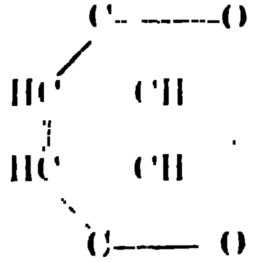
[1] Kekulé, *Annalen*, 1858, 106, 149.

[2] Couper, *Phil. Mag.*, 1858, IV., 16, 107.

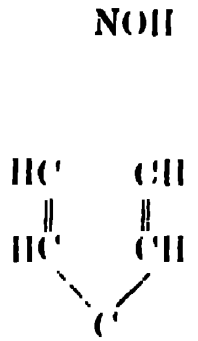
Thus, on the one side, we have Kekulé maintaining that graphic formulæ are mere shorthand symbols by means of which we can easily and compactly express the results of our chemical experiments; whilst, on the other side, Couper claims that these ciphers give us the key to the actual mode of linkage of the atoms within the molecule. Let us take each of these views in turn and see how far they can be brought into agreement with modern conditions.

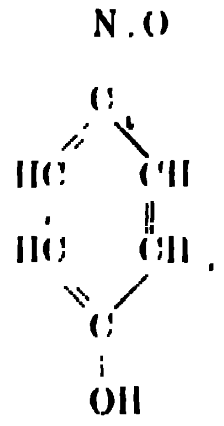
Regarded as pure reaction-formulæ, it must be admitted that our present symbols fail at too many points for our intellectual satisfaction. If we take the case of quinone as an example, we find that its formula is written in either of two ways—





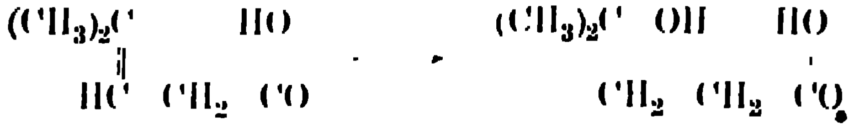
each of which is a representation of its method of reacting with a certain reagent. But neither of these formulæ allows us to foresee the fact that quinone monoxime will react as if it were nitroso-phenol—





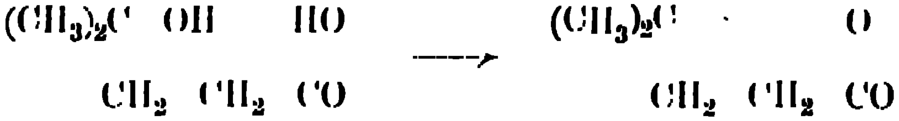
The number of facts of this type which have accumulated in recent years is considerable, and the result of this increase in knowledge has been remarkable. Instead of attempting to bring their formulæ into harmony with the facts, organic chemists have been content to drag behind them a lengthening chain of implications, which they read into a formula; *e.g.*, in the case of acetone and ethyl acetate we do not distinguish in our formulæ between the two carbonyl groups, but we mentally interpret the two symbols differently. Thus, at the present time, it is quite conceivable that a student may be well acquainted with the meaning of all the ordinary chemical symbols, but may be hopelessly at sea with regard to the behaviour of a given compound; though to a more experienced chemist this is implicitly expressed in the formula which misleads the beginner.

A concrete example will serve to bring out the amount of unexpressed material which we read into the ordinary formula. Let us consider the reactions of the unsaturated monobasic acids in presence of dilute sulphuric acid. In the first place, we assume that an addition of water to the double bond occurs—



$$\begin{array}{lll}\mathrm{(CH_3)_2C} & & \mathrm{HO}\\ \quad\Vert & & \\ \quad\mathrm{HC} & \mathrm{CH_2} & \mathrm{CO}\end{array} \longrightarrow \begin{array}{lll}\mathrm{(CH_3)_2C} & \mathrm{OH} & \mathrm{HO}\\ & & \quad\vert\\ \mathrm{CH_2} & \mathrm{CH_2} & \mathrm{CO}\end{array}$$

Now, we know from general experience that when one hydroxyl group lies in the 1,6-position to another in the same chain, water is usually eliminated with ease; so we should deduce that the next step in the process would be such an abstraction of a water molecule—

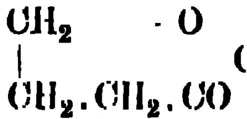


$$\begin{array}{lll}\mathrm{(CH_3)_2C} & \mathrm{OH} & \mathrm{HO}\\ \mathrm{CH_2} & \mathrm{CH_2} & \mathrm{CO}\end{array} \longrightarrow \begin{array}{lll}\mathrm{(CH_3)_2C} & & \mathrm{O}\\ \mathrm{CH_2} & \mathrm{CH_2} & \mathrm{CO}\end{array}$$

The formation of this compound is actually what does take place, so that in this case our implications are justified; but let us apply the same series of ideas to another instance. Take the case of vinyl-acetic acid (I.), which contains the double bond in exactly the same position as in the other substance. Applying our experience as before, we should deduce that the final product on heating with dilute sulphuric acid would be the lactone (II.) In practice no such substance is formed, the product being the new unsaturated acid (III.).

$CH_2:CH.CH_2.COOH$

(I.)



$$\begin{array}{l} CH_2 \quad \cdot O \\ | \\ CH_2.CH_2.CO \end{array}$$

(II.)

$CH_3.CH:CH.COOH$

(III.)

But this does not bring us to the end of the possible reactions of this class of substances; for if we take the case in which two methyl groups are attached to a different carbon atom we find that the reaction follows yet another course—

$$CH_2:CH.C(CH_3)_2.COOH$$

$$\searrow$$

$$CH_3.CHOH.C(CH_3)_2.COOH$$

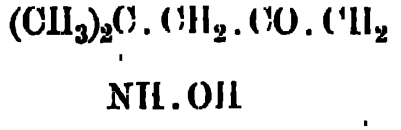
$$\searrow$$

$$CH_3.CH:C(CH_3)_2 + CO_2 + H_2O$$

Thus, our formulæ have ceased to be true reaction formulæ, and may merely serve to mislead us if we attempt to draw any general conclusions from them.

Let us now turn to Couper's view of formulæ, *viz.*, that they are to be regarded as true representations of the intimate structure of molecules. Here we appear to be upon safer ground; but again we meet with drawbacks. If a formula represents the actual mode of linkage of the atoms in a molecule, how can we be certain of our results when we apply chemical reagents to the compound? Quinone, when treated with hydroxylamine, behaves as if it contained a carbonyl radicle; but if we employ phosphorus pentachloride as our reagent it acts as if quinone contained a benzene nucleus, since *p*-dichlorobenzene results. In this case, what is the true structure of quinone? If it be regarded as an equilibrium mixture of two compounds or as existing in two vibration-phases, what becomes of our "intimate structure of the molecule"?

Evidently, from Couper's point of view, the outside reagent is a disturbing factor not allowed for in our formulæ. An example is furnished by the action of hydroxylamine upon mesityl oxide.[1] If the reaction is allowed to take place in a methyl alcoholic solution in presence of sodium methylate, the chief product is the substance formed by the addition of hydroxylamine to the double bond—



$$(CH_3)_2\underset{\displaystyle NH.OH}{C}.CH_2.CO.CH_3$$

But if, on the other hand, after exactly neutralizing hydroxylamine hydrochloride with sodium carbonate we allow it to act upon an alcoholic solution of mesityl oxide, we get the usual carbonyl group reaction, and mesityl oxime is formed—

$$(CH_3)_2C:CH.C(NOH).CH_3$$

Thus in *alkaline* solution the ethylenic bond is stimulated into activity, while in *neutral* solution the carbonyl radicle appears the more reactive of the two.

From this it becomes clear that in order to ascertain the true "intimate structure of the molecule" we must find some way of determining it apart from extraneous materials. How is this possible?

The recent developments in the study of physical properties of compounds indicate a means whereby the constitution of a body might be guessed without the necessity of applying disturbing reagents to it. At present our methods are not sufficiently advanced to permit us to establish molecular structure definitely by physical means alone; but even to-day we can accomplish a good deal with the help of absorption spectra, magnetic rotation, refractive index, magnetic susceptibility, electric absorption, optical rotatory power and dispersion; and there seems to be little reason to despair of further progress.

It is at this point that we encounter the difficulty which has been responsible for wrecking a considerable amount of work in recent years. On the one hand, as we have seen, stand our "chemical" formulæ which give us—incompletely enough, it must be confessed—a picture of the reactions of substances. On the other side, physical methods are showing us glimpses of the "intimate structure of molecules." Now a great mistake appears to have been made in assuming that both these things could be expressed by the same formulæ. Our old reaction-formulæ, though unable to cope with the difficulties in their own special field, have been imported willy-nilly into the problem of molecular structure, because we had nothing better to utilize there. The result has been something like the state of affairs which would reign in arithmetic if we insisted on using a mixture of Roman and Arabic notations in our calculations.

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[1] Harries and Lellmann, *Ber.*, 1897, 30, 230, 2726; Harries and Jablonski, *ibid.*, 1898, 31, 1371; Harries, *Annalen*, 1904, 330, 191.

It is evident that progress along these lines will be slow. What is required is that those investigators who concern themselves with physical properties should invent special symbols* to express their results, and should thus be freed from the implications which cling to the ordinary formulæ. Then, at a later stage, it may be possible, with increased knowledge, to harmonize the two symbolical systems and produce a combined notation which will include the valuable parts of each.

Unfortunately, there seems little doubt that this suggestion will be ignored. Conservatism is ingrained in most scientific minds; and the struggle which new ideas have before them is generally severe.†

We must now turn to another region wherein our modern formulæ are failing to meet the demands made upon them. When we examine the matter closely, we find that the foundations of theoretical organic chemistry are a series of labels by means of which we endeavour to conceal our ignorance of the fundamental phenomena of the subject. Of these labels, none is used more indefinitely and at random than the word "Unsaturation." What do we mean by an unsaturated compound? It may be defined as a molecule which, without total disruption of its original structure, is capable of uniting with one or more fresh molecules.

Now when we consider unsaturation in its broadest aspects, it is evident that what we call unsaturation is a specific and not a general property. We represent the unsaturation of an ethylenic linkage and of a carbonyl radicle by the same symbol, a double bond; and as far as the action of nascent hydrogen is concerned, this is quite accurate, for both the ethylenic linkage and the carbonyl group will attach to themselves two atoms of hydrogen. But when we use bromine instead of hydrogen, we find that only the ethylenic linkage reacts; for the carbonyl radicle remains unaffected by the reagent.

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* The electronic symbols suggested by Nelson and Falk represent something akin to what is intended; though in their present form they cling too closely to ordinary formulæ.

† An amusing example of this is to be found in Kolbe's review of van't Hoff's theories on their first publication.

Thus we cannot say definitely that the ethylenic linkage is more or less active than the carbonyl bond; for the matter is influenced in different ways by the reagent employed, the solvent used, and the relative position of the two double bonds in the molecule. In other words, "unsaturation" is not a definite, measurable thing which we can predict in any case from the behaviour of the "unsaturated" substance in other circumstances; it is rather something kinetic, something which is extremely sensitive to external forces, and which in its turn can play a part in influencing the chemical action of groups which it does not apparently affect directly.

As an example of this latter property we may quote the case of the Vorländer Rule.[1] Vorländer has pointed out that we can consider both acids and alcohols as derived from water by substitution. In the case of acetic acid we substitute an acetyl group for one of the hydrogen atoms of water, while ethyl alcohol is formed from water by the substitution of an ethyl group for a hydrogen atom—

$$H{-}OH \qquad CH_3.CH_2{-}OH \qquad CH_3.CO{-}OH$$

When we examine the chemical behaviour of the hydrogen atom in each case, we find that in the acids it has a much greater activity than in the alcohols. The origin of this difference obviously lies in the difference between the acyl and alkyl groups to which the hydroxyl radicle is united. The question is commonly dealt with by labelling the acyl group "electro-negative," and treating the label as an explanation. But, as Vorländer pointed out, this case is only one example of a general rule. If we represent non-metallic elements by E, and write down the following series:—

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[1] Vorländer, *Ber.*, 1901, **34**, 1633.

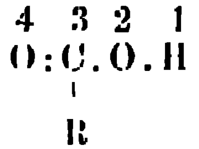
$$\overset{1}{H}.\overset{2}{E}.\overset{3}{E}:\overset{4}{E}$$

$$\overset{1}{H}.\overset{2}{E}:\overset{3}{E}$$

$$\overset{1}{H}.\overset{2}{E}.\overset{3}{E}.\overset{4}{E}:\overset{5}{E}$$

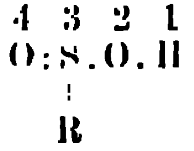
we shall find that the hydrogen atom in the first line has a greater reactivity than those in the second and third lines; in the first case the double bond between two E atoms lies in the 3 : 4 position to the labile hydrogen atom, while, where the double bonds are in the 2 : 3 or 4 : 5 positions the hydrogen atom is not specially reactive. For example, the labile hydrogen atoms in oximes, acids, phenols, diazo-compounds, and sulphinic acids are all situated as in the first type with respect to the double bond—

$$\overset{4}{R}.\overset{3}{CH}:\overset{2}{N}.\overset{1}{O}.H$$

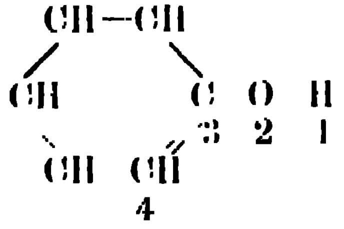


$$\overset{4}{O}:\overset{3}{\underset{R}{\underset{|}{C}}}.\overset{2}{O}.\overset{1}{H}$$

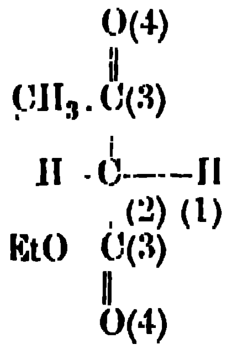
$$R\ \overset{4}{N}:\overset{3}{N}.\overset{2}{O}.\overset{1}{H}$$

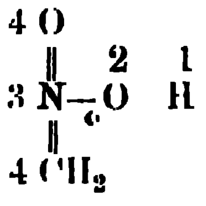


$$\overset{4}{O}:\overset{3}{\underset{R}{\underset{|}{S}}}.\overset{2}{O}.\overset{1}{H}$$

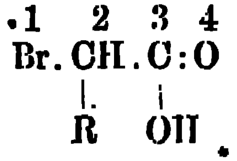


In aceto-acetic ester and nitro-methane the hydrogen atoms are doubly influenced—

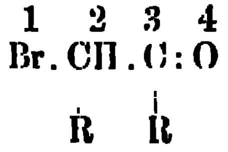




Further, when an acid or a ketone is brominated, the halogen atom enters the nucleus in the position required by this rule, *i.e.* it replaces the hydrogen atom in the α-position to the carbonyl group—

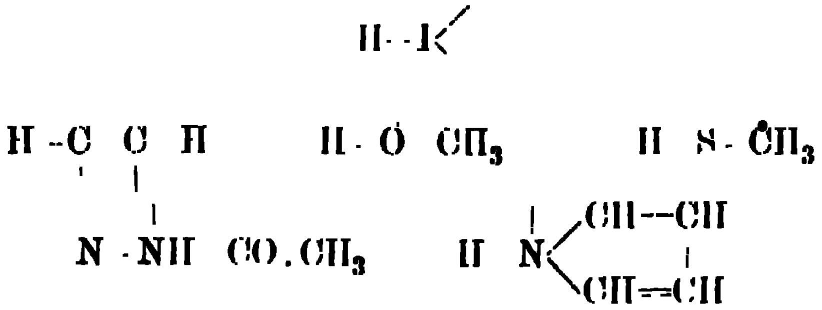


$$\overset{1}{\mathrm{Br}}.\overset{2}{\underset{\underset{\displaystyle\mathrm{R}}{|}}{\mathrm{CH}}}.\overset{3}{\underset{\underset{\displaystyle\mathrm{OH}}{|}}{\mathrm{C}}}:\overset{4}{\mathrm{O}}$$



$$\overset{1}{\mathrm{Br}}.\overset{2}{\underset{\underset{\displaystyle\mathrm{R}}{|}}{\mathrm{CH}}}.\overset{3}{\underset{\underset{\displaystyle\mathrm{R}}{|}}{\mathrm{C}}}:\overset{4}{\mathrm{O}}$$

There seems to be another influence at work in the case of acidic hydrogen atoms; and as the matter appears to have escaped notice hitherto, it may be well to call attention to it in this connection.[1] An examination of the formulæ of those substances which are capable of yielding metallic derivatives by direct displacement of a hydrogen atom will show that the atom to which the labile hydrogen is attached is capable of exerting a valency higher than that which it exhibits in the acidic compound. For example, in the following substances the oxygen and sulphur atoms are divalent, while both oxygen and sulphur are capable of acting as quadrivalent elements; carbon in acetylene acts as a divalent atom, though its maximum valency is four; the nitrogen atoms shown below are trivalent, but nitrogen can act as a pentad; iodine can act either as a mono- or a trivalent element. The formulæ are written with lines to show the extra valencies—



It will be seen that this is of more general application than the Vorländer Rule, for it holds in the case of substances such as ethylates, whose formation takes place though there is no double bond in the molecule such as is required by Vorländer's view. In fact, the structure demanded by the Vorländer Rule is merely a reinforcing influence upon the lability of the hydrogen which already exists owing to the presence of the atom capable of showing a rise in valency.

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[1] Smiles, *Trans. Chem. Soc.*, 1900, 77, 160.

We must now turn to another point of view. Hitherto we have regarded unsaturation from the standpoint of addition reactions, but we may now extend this a little. Suppose that we have two isomeric substances, each capable of taking up four bromine atoms, are these two bodies equally saturated or are they not? The question of unsaturation here resolves itself into one of stability. We cannot distinguish between the bodies by the *amount* of bromine they take up, so we seek some other criterion. Now, in the case of two substances, one of which has a pair of conjugated double bonds, while in the other the bonds are not so related, the first substance takes up the four bromine atoms two by two, but the second one takes up all four simultaneously. The action is thus more precipitate in the second instance, and we should be tempted to consider the first substance as the less unsaturated of the two. In fact, as Thiele put it, the conjugated double bonds partially saturate one another.

Further, when an unsaturated acid is brought into conditions which allow it to undergo isomeric change, it is almost always converted into the form which contains the ethylenic bond conjugated with that of the carboxyl group. Evidently, then, this grouping must be the most exothermic, and therefore the most saturated.

We may now sum up, as far as possible, the various points which we have treated in the foregoing pages. We have shown, in the first place, that unsaturation is not an intrinsic property of any molecule. It depends largely upon the nature of the outside reagent; in order to have "unsaturation" we must have two substances, each specially fitted to interact with the other. In fact, the addition reactions of organic chemistry appear to be an extreme case of the ordinary reaction of salt formation, such as takes place in the case of ammonia and acid. Secondly, the influence of the other (non-reacting) parts of the molecule may play a very considerable part in any addition reaction, so that we cannot ascribe the same meaning to every double bond that we write down. For example, since the ethylenic bond in maleic acid refuses to react with hydroxylamine, it must be chemically quite different from that in mesityl oxide which reacts readily in alkaline solution. Thirdly, just as unsaturation can be influenced by neighbouring unsaturations, it may in turn exert an influence upon groups of atoms in its vicinity. And, finally, if we have a series of unsaturations in a molecule they can be made to rearrange themselves to form a more stable system.

It is especially in this region of unsaturation that we find the limitations of our structural formulæ most clearly marked. When we write a double bond between two atoms, we do not always mean the same thing. The double bonds in the cases of diphenyl-ethylene, ethylene, and fulvene certainly do not resemble one another chemically: in the first case the double bond is not attacked by bromine, which is taken up easily by the double bond of ethylene; but while the fulvene series are oxidized by air, ethylenic substances are not. Thus we have an increase in unsaturation (or reactivity as regards bromine and oxygen) as we go from diphenyl-ethylene through ethylene to the fulvenes; yet we symbolize all three unions between the carbon atoms of the double bonds in exactly the same way. It is perfectly evident that the amount of reactivity is different in these three cases, and therefore the "chemical affinity," which gives rise to the reactions, must be different also.

But it is not only in the case of the double bond that we can trace this alteration in value of valencies; we can discover it in the case of single bonds as well. It is well known that in bromo-benzene, the bromine atom is held to the carbon atom of the nucleus more firmly than is the case in aliphatic bromine derivatives. But if we nitrate the benzene ring, the bromine in the aromatic bromine derivative becomes as labile as that in the aliphatic one. This increase in reactivity can be due only to some change in the force which holds together the carbon and bromine atoms; in other words, the "valency-force" uniting bromine to carbon is stronger in bromobenzene than in nitro-bromobenzene.* Flürscheim[1] has carried out some experiments by means of which he showed that this variation in the value of the single bond is quite a general property.

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* When the above paragraph was written in 1908, I was under the impression that this had long been common knowledge. Dr. Flürscheim desires me to mention, however, that he published a paper on the point in 1906 (*Ber.*, **39**, 2016).—A. W. S.

[1] Flürscheim, *J. pr. Chem.*, II., 1902, **66**, 329; see also Werner, *Ber.*, 1906, **39**, 1278.

It may be supposed by some that if we accept these ideas we shall be taking a retrograde step, and plunging ourselves into a web of inconsistencies; but surely it is not so! At the time of Frankland, chemists had not acquired those ideas of chemical structure which we now possess, and which we cannot abandon without having something better to take their place; consequently, it was necessary for the science to go through a stage in which valency was regarded as a fixed, unalterable force; without this guiding principle the work of the last forty years would have been impossible.[1] But we have now reached a point from which we can look back and enlarge our views without running the risk of losing hold of what we have acquired. Instead of considering a "bond" as a fixed unit, we can regard it rather as the sum of an almost infinite number of small forces; so that we can subtract from or add to its strength within limits without bringing it out of the category of a "bond" or valency. For example, if the force employed in uniting two atoms together by means of a single bond be termed "F^2," then the quantity F will be negligible in comparison with the force of the single bond. But it is quite conceivable that this small force F would be sufficient to cause a difference of *reactivity* according as it were added to or subtracted from the force F^2. Thus the two forces expressed by $F^2 + F$ and $F^2 - F$ would not differ appreciably in their capacity for uniting two atoms, and certainly would not be so different as to allow the first atom to unite with two others; yet at the same time they would be sufficiently different to produce a change in reactivity of an atom attached to another by one or other of them.

From this point of view, investigations of the reactivities of certain atoms and groups in molecules are of the greatest importance. A considerable amount of work[2] in this direction has already been carried out; but a vast field lies open to research in this branch of the subject. With an increase in our knowledge of the factors which govern the reactive power of compounds must come, in the end, a modification of our structural formulæ.

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[1] An interesting paper by Tschitschibabin (*J. pr. Chem.*, 1912, 86, 381) on "The Valency of Carbon Atoms in So-called 'Unsaturated' Compounds" may be brought to the notice of the reader in this connection.

[2] See among others, Clarke, *Trans.*, 1911, 99, 1432; 1912, 101, 1788; Harper and Macbeth, *Trans.*, 1915, 107, 87; Macbeth, *ibid.*, 1824; Petrenko-Kritschenko, *J. pr. Chem.*, 1900, [2], 61, 431; Petrenko-Kritschenko and Kantschoff, *Ber.*, 1906, 39, 1452; Sonter, *Trans.*, 1909, 95, 1827; *ibid.*, 1910, 97, 1623; Stewart, *Trans.*, 1905, 87, 185, 410.

We are now in a position, not, certainly, to forecast the character of the symbols which will replace our present ones, but to state clearly what functions these symbols will have to fulfil if they are to be regarded as satisfactory. They will have to cover the reactions which compounds undergo and to do this better than our present notation permits. They will have to indicate in some manner the reactivity of the compound, as distinct from the mere power of entering into reactions. And, finally, they will have to embody the knowledge of the intimate structure of molecules which we may in future obtain.

It is not to be expected that success will be attained at a stroke. Much more probably, there will be a good deal of fumbling and recasting to be gone through, just as there was before our present-day formulæ emerged from the melting-pot. Any suggestions, therefore, which tend towards the enlargement of our ideas of chemical constitution should be welcomed by those who have sufficient critical spirit to grasp the failure of our contemporary formulæ under the strain of modern investigation.

CHAPTER XIV

SOME UNSOLVED PROBLEMS

In the foregoing pages many examples have been given to illustrate the surmounting of difficulties, either practical or in theory, which at first sight appeared insuperable; and a study of the countless successes which have been achieved by organic chemists in the solution of the problems of chemical constitution cannot fail to raise sanguine hopes that in the future the most complicated structures will be elucidated. Yet it must be freely admitted that even the simplest compounds and reactions remain fruitful fields for further investigation; for it is precisely in this region that modern organic chemistry is most backward. Whilst the frontier of the subject is being pushed ever onward, the older branches remain very much where the pioneers left them; and our knowledge of fundamental things has not increased at anything like the same rate as our other acquirements. In the present chapter, an attempt will be made to direct attention to a few of the many points which might repay further thought and experiment.

In the first place it may be asked why carbon, among all the elements, stands pre-eminent in its capacity for forming long atomic chains. Other elements also are capable of catenation; but none of them shows this peculiarity so markedly as carbon.

Chain-formation appears to be a characteristic confined to those elements which lie close to carbon in the Periodic Arrangement of the elements, the metallic elements being almost devoid of the catenating property. Thus while boron forms various hydrides of which the most complicated[1] appears to be $B_{10}H_{14}$, the next element in the group, aluminium, has no capacity for chain-formation. Carbon, in the fourth group, appears to have an almost unlimited facility in forming long chains of atoms; but its next analogue, silicon, has up to the present yielded nothing higher than the six membered chain[1] in hexasilane, Si_6H_{14}, while the third and fourth members of the group, titanium and germanium, exhibit no catenating properties at all, and the tin phosphide, Sn_9P, seems hardly a parallel case.[2] In Group V., nitrogen, especially when associated with carbon atoms, manifests a considerable power of chain-formation; phosphorus[3] reaches its maximum in the compound $P_{12}H_6$; arsenic is limited to the union of two atoms and forms no hydride[4] more complex than As_2H_2; whilst the remaining members of the group show no tendency towards forming chains. Turning to Group VI., oxygen forms a three-membered chain in ozone; but except in organic compounds[*] the higher limit for the remainder of the group appears to be two atoms in the chain in such compounds[5] as H_2S_2. In the halogen group, the only tendency towards catenation is to be found in the somewhat doubtful examples of such compounds as KF : FH.

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[1] Stock, Friederici, and Priess, *Ber.*, 1913, **46**, 3353.

From this survey it will be evident that carbon atoms possess some peculiar property which enables them to excel all others in this direction; and, further, that only those atoms in the immediate neighbourhood of carbon in the Periodic Arrangement (boron, silicon, nitrogen, and phosphorus) have the chain-forming property developed to any marked extent. It is natural to inquire why this should be so. There is at present no explanation capable of accounting for the phenomena; but there are sundry facts which appear to have some possible bearing upon the question.

In the first place, the presence of metallic characteristics in an atom appears to be a bar to chain-formation upon an extended scale, since otherwise there seems to be no reason why aluminium, for example, should not yield more complex derivatives than it actually does. It is obvious that the linkage which unites two atoms in a molecule capable of hydrolytic dissociation must be weaker than that which holds together such a pair of atoms as carbon and chlorine; and since the metallic atoms are all capable of forming easily dissociable compounds it appears not unlikely that the form of linkage affected by them is of a slighter character than that which carbon exerts. Possibly this factor enters into the question of chain-formation, or at least chain-stability. Suggestions have been put forward that valency may be divided into two categories: polar and non-polar; and perhaps considerations of this type,[1] when carried further, may bring to light the true explanation of the catenating properties of certain classes of atoms.

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[1] Stock and others, *Ber.*, 1916, **49**, 108, 111; 1917, **50**, 1739, 1754, 1764; 1918, **51**, 989.

[2] Stead, *J. Soc. Chem. Ind.*, 1897, **16**, 200.

[3] Besson, *Compt. rend.*, 1890, **111**, 972; Stock, Böttcher, and Lenger, *Ber.*, 1909, **42**, 2839, 2847.

[4] Janowsky, *Ber.*, 1873, **6**, 220.

[*] Among the organic compounds cases have been discovered in which no less than five sulphur atoms appear to be united in a straight chain—*e.g.* benzene sulphonic trisulphide, $C_6H_5 . SO_2 . S . S . S . SO_2 . C_6H_5$ (Tröger and Hornung, *J. pr. Chem.*, 1899, **60**, 134). The extreme case appears to be tolyl pentasulphide, $CH_3 . C_6H_4 . S . S . S . S . S . C_6H_4 . CH_3$. (Tröger and Voigtländer, *J. pr. Chem.*, **54**, 513).

[5] Bloch and Hohn, *Ber.*, 1908, **41**, 1971.

Secondly, all the catenating elements dealt with above are of the "amphoteric" type, that is, they are capable of combining directly with either electropositive hydrogen or electronegative chlorine; but it should be noted that of them all, carbon is the only one which forms equally stable derivatives with both these elements.

Thirdly, all these chain-forming elements are marked by their comparatively small atomic volumes;* and it is not without interest to note that those other elements which, while incapable of chain-formation, show a tendency towards complex salt formation, are also of small atomic dimensions. An examination of the atomic volume curve will show that carbon has the smallest atom of all the elements; and it seems not improbable that this peculiarity is in some way connected with its extraordinary capacity for catenation.†

Thus if we gather together the chief characteristics of those elements which form chain-compounds, it appears that they: (1) have no metallic properties; (2) are amphoteric in character; and (3) have small atomic volumes. What lies behind this must be left for speculation to suggest.

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[1] See Friend, *The Theory of Valency*; Blomstrand, *Chemie der Jetztzeit*, 1869, pp. 217, 243; Hinrichsen, *Zeitsch. physikal. Chem.*, 1902, 39, 305; Abegg, *Zeitsch. anorgan. Chem.*, 1904, 39, 330; Spiegel, *ibid.*, 1902, 29, 365; Friend, *Trans.*, 1908, 93, 260; De, *Trans.*, 1919, 105, 127; Briggs, *ibid.*, 278.

* The atomic volume of nitrogen is abnormal, as an examination of the curve will at once show.

† This suggestion was made to me in 1910 by the late Lieutenant C. R. Crymble.

Turning now to a different field, it is natural to inquire why the introduction of a cyclic grouping into a molecule should produce the changes in chemical character which are well known to follow ring-formation. For example, it is hard, on our modern assumptions with regard to the nature of atoms and molecules, to regard molecular structure as a rigid thing; yet in the case of cis-trans cyclic stereoisomers * there appears to be a fixity in the relative positions of atomic groups which seems to point to some "stiffening" of the forces binding the atoms in position. In fact, in this case, the purely mechanical model with its fixed and rigid bonds, gives on the whole the best representation of the phenomena which has yet been devised. Yet it is clear that there can be nothing in the nature of this within the molecule itself. The idea of Faraday tubes connecting atom with atom may to some extent assist us to harmonize the mechanical model and the actual atomic properties; but up to the present it may be said that we have no clear conception which fits the facts exactly and sufficiently.

In the group of cyclic compounds, another unexplained phenomenon meets us at once: the benzenoid character possessed by certain substances. This peculiar series of properties is evidently not produced by one factor alone, but must be the result of at least three co-existing influences. The alternating system of double and single bonds which is characteristic of the benzene system is to be found in other molecules as well. It occurs, for example, in hexatriene: $CH_2 : CH . CH : CH . CH : CH_2$; but no aromatic character is shown by this substance. Again, the mere occurrence of a six-membered ring in a compound confers no benzenoid characteristics on the substance, as is seen in the case of the terpenes or the hexamethylene derivatives. Finally, even the combination of a ring and the alternate grouping of single and double bonds does not suffice to produce aromatic properties, since both such characteristics are present in cyclo-octatetraene :—

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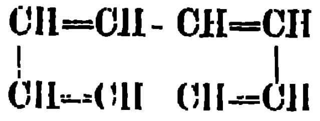
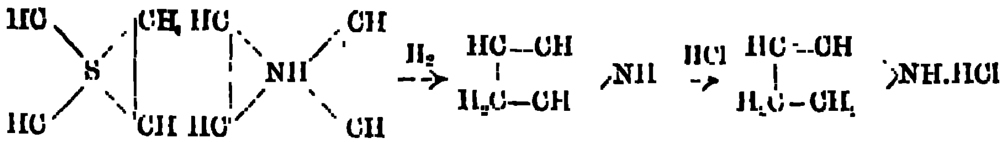
* And also, though to a lesser extent, in ethylenic stereoisomers.



and yet this substance[1] is not benzenoid in character. It is thus evident that the *number* of the carbon atoms in the ring must have some influence; and that to possess the aromatic characteristics a compound must contain: (1) a cyclic structure; (2) six atoms in the ring; [*] (3) a symmetrical arrangement of alternate double and single bonds within the ring. Why this particular arrangement should be required and why it and only it can confer aromatic properties upon a hydrocarbon molecule is a point upon which speculation has hitherto failed to throw light. The most plausible solution is to be found in Collie's benzene space-formula;[2] but even it leaves room for further thought on the subject.

The resemblance to the benzene characteristics which is exhibited by thiophene is another point upon which no satisfactory views have been expressed. It may be recalled that although the usual formulæ for thiophene and pyrrol contain atoms capable of forming "onium" derivatives by the addition of alkyl iodides, no such addition reaction has been observed in either case. If, however, pyrrol be reduced to dihydro-pyrrol, the nitrogen atom apparently becomes normal in this respect; and ammonium salt formation takes place. This behaviour could be expressed by means of the following formulæ:—



Thiophene. Pyrrol. Pyrrol

but in view of other reactions it seems doubtful if this view can be maintained.

We come next to addition reactions; and in this class many problems present themselves for solution. The most general rule which has been laid down in the field goes by the name of

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[1] Willstätter and Waser, *Ber.*, 1911, **44**, 3423.

[*] It should be noted that in such substances as pyridine, atoms other than carbon ones can form part of the ring and still the benzenoid character is maintained to a great extent.

[2] Collie, *Trans.*, 1897, **71**, 1013.

Michael's Distribution Principle.[1] Suppose that we have an unsaturated molecule which can be represented by A—B and that another molecule C—D can attach itself to the first one; then it is clear that we might have either C—A—B—D or D—A—B—C produced as the result of the reaction. Suppose that the forces attracting A to C be represented by *ac*, while those attracting A to D are symbolized by *ad*, etc., then it is clear that if *ac* + *bd* is greater than *bc* + *ad*, then the compound C—A—B—D will be produced in greater yield than the compound D—A—B—C.

This "principle" of Michael, however, does not go far enough to bring into line all the relevant facts. The addition of hydrobromic acid to a compound of the type $CH_2:C(CH_3)_2$ results mainly in the production of $CH_3.CBr(CH_3)_2$ wherein the halogen atom has attached itself to the tertiary carbon atom. It is impossible to dissociate this in one's mind from the fact that bromination of the compound $CH_3.CH(CH_3)_2$ leads as a main reaction to the formation of $CH_3.CBr(CH_3)_2$, wherein the tertiary carbon atom is again attacked. Obviously there is some peculiar quality in the tertiary grouping which renders it attackable; for the paraffin $CH_3.CH(CH_3)_2$ is as easily oxidized as an olefine by means of potassium permanganate.[2]

This behaviour of a purely aliphatic compound is sufficient to show that the similar reactivity of the "tertiary" atom in triphenylmethane is not due to the influence of the phenyl radicles in the molecule, but depends upon some much simpler factor.

The addition reactions of the aldehydes appear to furnish ground for investigation. There is an obvious parallelism between the methods of addition in the cases of such dissimilar reagents as hydrocyanic acid, potassium bisulphite, ammonia, and the Grignard reagent; for in each process the free hydrogen atom (or the —Mg. I group of the Grignard reagent) attaches itself to the oxygen atom of the aldehyde, while the remainder of the entering molecule fastens itself upon the carbon atom of the carbonyl group. Abegg[3] has tried to account for the

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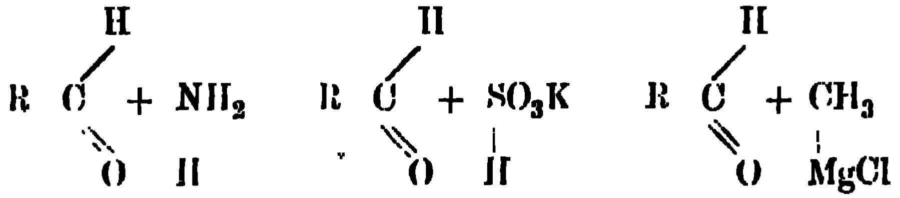
[1] Michael, *J. pr. Chem.*, 1888, II., 37, 524; 1899, 60, 286, 409; 1903, 68, 487; *Ber.*, 1906, 39, 2138.

[2] Zelinsky and Zelikow, *Ber.*, 1901, 34, 2865.

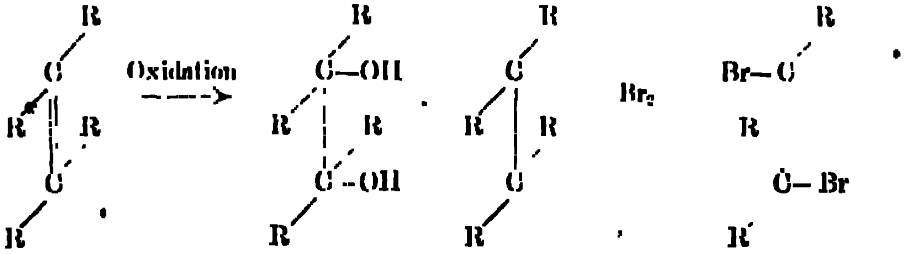
[3] Abegg, *Ber.*, 1905, 38, 4112.

Grignard reaction by assuming that in $CH_3 . Mg . Cl$ the group Mg. Cl is "positive," whilst the methyl group is "negative." This seems to be a mere juggling with words; and it certainly fails to account for the fact that the groups $—NH_2$ and $—SO_3K$ appear to have exactly the same "polarity" as the methyl group must have on his hypothesis:—



since they behave in precisely similar manners in their reactions with the aldehyde molecule. It is evident that the solution of this problem is still to be sought.

Another field of inquiry in addition reactions is that opened up by the discovery that oxidizing agents and halogen molecules appear to act in entirely different ways upon unsaturated linkages.[1] The oxidizing agent attacks a single "side" of the molecule, whereas the halogen atoms attach themselves in the trans-position as shown below:—



Cis-addition. Trans-addition.

Frankland[2] has suggested that this may be due to the atoms in a halogen molecule being separated by a distance sufficient to bring them on opposite sides of the ethylenic molecule when they react with it. Stewart[3] ascribes the phenomenon to a non-simultaneity in the addition-reaction in the case of the two carbons united by the ethylenic linkage. Thus if one carbon atom is attacked before the other, there will momentarily be formed the grouping—

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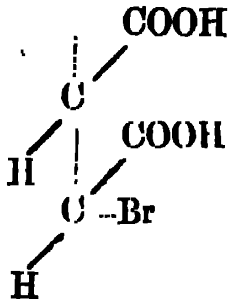
[1] Michael, *J. Amer. Chem. Soc.*, 1918, **40**, 704, 1674.

[2] Frankland, *Trans.*, 1912, **101**, 673.

[3] Stewart, *Stereochemistry*, 1919, p. 118.



and the final situation of the second bromine will be determined by the directive forces which this complex exerts upon the entering atom. In Stewart's view, these forces tend to drive the incoming atom into the trans-position. The phenomenon is to some extent akin to that of the Walden Inversion.

Other examples of analogous "directing" agencies are to be found in the phenomena of the Crum Brown Rule * and in the field of stereochemistry. Thus in the case of the esterification of an active acid with an alcohol it is found that the rate of reaction between the *d*-acid and the *d*-alcohol is different from that of the reaction between the *d*-acid and the *l*-alcohol; similar results are observed in the case of the breakdown of active materials by means of active catalytic agents; and the influence of directive factors in the case of asymmetric syntheses is obvious. Up to the present, there is no "explanation" of these things.

In a similar class we may place those cases wherein the same reagent acts differently upon molecular structures which we symbolize by identical signs. For example, we write the same symbol for a double bond whether it be present in an ethylenic linkage, a carbonyl radicle, or a carbon-nitrogen union; yet these three types differ entirely from each other in their behaviour towards hydrogen and bromine. It may be objected that although the bonds are written in the same way, we mentally interpret them differently according to the atoms which they join; but as we have already seen,† even the ordinary ethylenic bond is used to cover a number of cases wherein the reactions of the compounds are not even remotely alike.

Molecular stability is another problem of which barely the fringe has been surveyed. Why is the compound (I.) extremely stable while (II.) is unstable and (III.) is non-existent under the same experimental conditions?

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* See p. 13.

† See p. 325.

$$C_6H_5—N:N—C_6H_5 \quad (I.) \qquad C_6H_5—N:N—OH \quad (II.)$$

$$CH_3—N:N—OH \quad (III.) \qquad C_6H_5—P:P—OH \quad (IV.)$$

No satisfactory theory of this apparently simple problem has yet been suggested, nor have we any hypothesis which accounts for the non-isolation of the phosphorus analogue (IV.) of diazobenzene hydrate.

Again, carbonic acid is unstable; but when a sodium atom is substituted for one of the hydrogen atoms the resulting sodium bicarbonate is quite a stable compound. The same rule holds good in the case of the analogous sulphur derivative, sulphurous acid. Yet in each case the salt is more strongly dissociated than the parent acid in aqueous solution.

There appears to be some influence at work which prevents the accumulation of certain atomic groups upon one carbon atom. Thus although tetrachloromethane, CCl_4, and tetranitromethane, $C(NO_2)_4$, are compounds which can be distilled without decomposition at ordinary pressure, the analogous tetra-amino-derivative, $C(NH_2)_4$, is unknown; and reactions leading to its formation produce only guanidine $NH:C(NH_2)_2$. In the case of four hydroxyl radicles attached to one carbon atom the decomposition goes even further; the compound $C(OH)_4$ breaks down instantaneously in order to yield carbon dioxide and water.

In a minor degree this instability can be traced in certain other reactions. Chloroform is unaffected by alkali bisulphites, whereas chloropicrin reacts readily to yield trisulphonates such as $H.C(SO_3K)_3$, so that evidently the introduction of the nitro-group has lowered the stability of the compound.

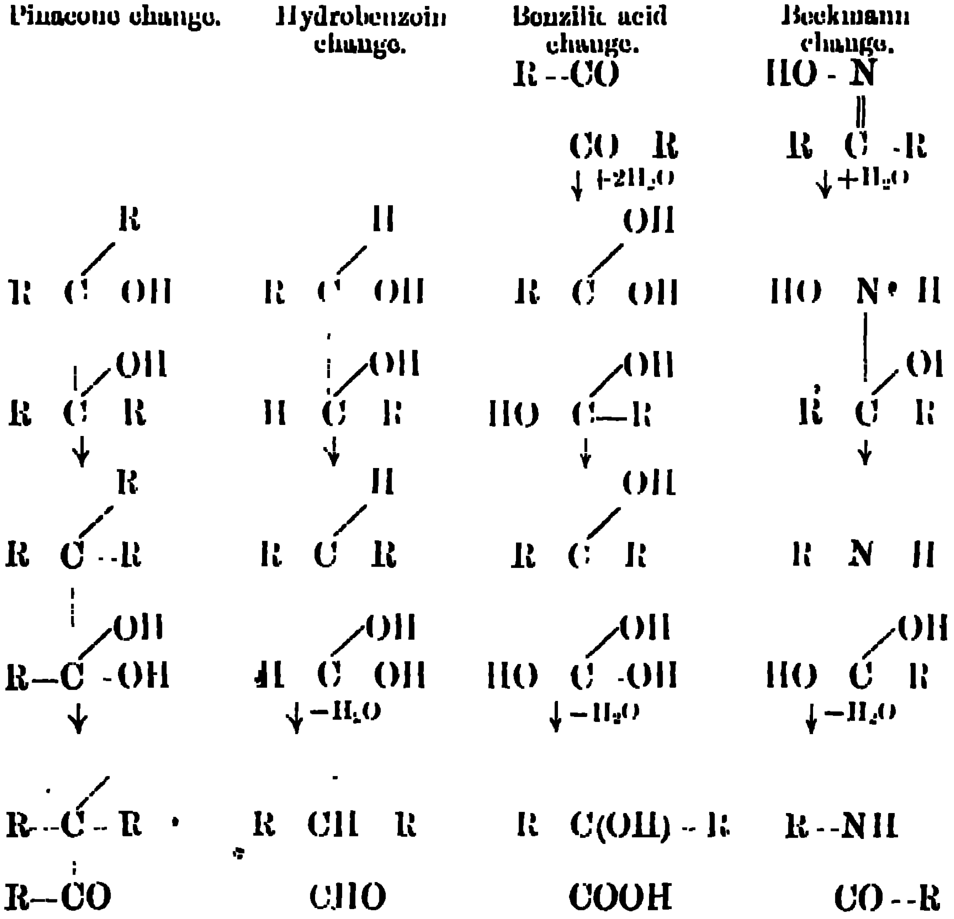
As an offset to this, the stabilizing action of a chlorine substituent may be noted. At ordinary temperatures acetaldehyde forms no stable addition product with water; whereas the hydrate of chloral is comparatively stable:—

$$\underset{\text{Unstable.}}{CH_3.CH(OH)_2} \qquad \underset{\text{Stable.}}{CCl_3.CH(OH)_2}$$

It appears that an extension of our knowledge of the stabilizing and unstabilizing influences of various substituents in methane might open up a very interesting line of research.

Intramolecular change* furnishes one of the most interesting fields for speculation in organic chemistry. Two problems are evidently involved in the question: for we may inquire, in the first place, why one particular structure is more stable than an isomeric form; or, secondly, we may endeavour to conjecture the mechanism of the process whereby the one isomer is converted into the other. Let us take certain well-known examples of intramolecular changes and see if they can be accounted for by any general principle. It will be sufficient if we examine the pinacone change, the Beckmann rearrangement, the benzilic acid change, and the hydrobenzoin change.

All these four types of rearrangement within the molecule can be brought into line if it be assumed that the first stage in the reaction consists of the addition of an outside reagent, which for the sake of simplicity we may regard as water. The changes would then be expressible as shown below; and the parallelism between them is obvious at a glance:—



Pinacone change. Hydrobenzoin change. Benzilic acid change. Beckmann change.

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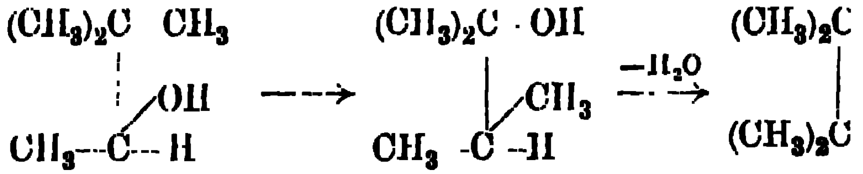
* For some general views on intramolecular change see Lapworth, *Trans.* 1898, 73, 445; and Tiffeneau, *Revue gen. d. Sciences*, 1907, 583.

The fact that all four reactions can be represented in a common system seems to point to the probability that this view of the mechanism may be near the truth; and it is therefore worth while to examine the matter rather more closely. When we look at the intramolecular rearrangements demanded by this formulation, it is clear that in each case there is a tendency to accumulate hydroxyl radicles upon a single carbon atom instead of allowing them to remain distributed evenly throughout the molecule. Such a grouping is unstable, as is well known; so that once it is formed it would be liable to break up, and would not be reformed to any extent by a back-reaction.

The conversion[1] of pinacoline alcohol, $(CH_3)_3C.CH(OH).CH_3$, into symmetrical tetramethyl-ethylene, $(CH_3)_2C:C(CH_3)_2$. is evidently another process wherein some intermediate stage must occur; since the direct elimination of water would lead by analogy to some such compound as $(CH_3)_3C.CH:CH_2$. Possibly the course of the reaction is as shown below:—



The inertness of the carbonyl radicle in compounds such as acids, acyl chlorides, amides and imides is very striking, especially when the marked reactivity of the ketonic group in pyruvic acid is borne in mind. In this case there can hardly be any "positive" or "negative" property of the substituent involved: a chlorine atom paralyses the carbonyl group whilst the equally "negative" carboxyl radicle in no way interferes with the carbonyl reactions; while the "positive" amido-radicle has the same effect as the "negative" halogen atom.

In concluding this chapter it may be well to draw attention to a number of specific cases[2] which require further investigation. Some of these may be mere examples of polymorphism, but there are others which cannot be accounted for upon any such hypothesis.

From viscosity measurements,[3] it appears that nitrobenzene exists in two different forms, though the spectra of these appear to be identical.[1] There are two forms of *o*-nitrotoluene, *o*-chlorotoluene, *o*-bromotoluene, *o*-toluidine,[2] and *o*-chloroaniline.[3] Two forms of benzophenone exist; and numerous other examples are quoted by Knoevenagel.[4]

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[1] Zelinski and Zelikow, *Ber.*, 1901, **34**, 3250.

[2] I am indebted to Professor Smiles for some of the following examples.

[3] Mühlenbein, *Ueber die innere Reibung von Nichtelktrolyten*, p. 57.

Two varieties of 4-quinolinic acid appear to have been isolated which form different salts. Dihydroxy-dinaphthol sulphide exists in two forms which differ from each other in the reactivities of the hydroxyl groups and sulphur atoms.[5] A similar case has been observed in 1-chloro-4-nitronaphthalene, wherein the chlorine atoms have quite different activities in the two varieties. The more complex phenanthrene nucleus exhibits analogous phenomena, for 3-phenanthrylamine[6] exists in two forms each of which gives rise to a characteristic series of salts which on decomposition regenerate the isomer from which they were prepared, although both forms of the parent amine give rise to identical acetyl derivatives.

Enough has now been said to show that even among the simplest problems of organic chemistry there remains, despite all the work of the past fifty years, an extremely fascinating field of inquiry. It is one which especially lends itself to the propounding of hypotheses; but it should be remembered that unless an hypothesis suggests lines of further research it is in itself likely to be of little value except as a help to the memory in grouping the known facts in a simpler form.

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[1] Crymble, Stewart, and Wright, *Ber.*, 1910, **43**, 1183.

[2] Ostromisslensky, *Zeitsch. physikal. Chem.*, 1906, **57**, 341.

[3] Knoevenagel, *Ber.*, 1907, **40**, 508.

[4] Knoevenagel, *Entwicklung d. Stereochemie zu einer Motostereochemie*, 1907, p. 213.

[5] Henriques, *Ber.*, 1894, **27**, 2993; Christopher and Smiles, *Trans.*, 1912, **101**, 710; Crymble, Ross, and Smiles, *ibid.*, 1146; Nolan and Smiles, *ibid.*, 1420.

[6] Werner and Kuntz, *Ber.*, 1901, **34**, 2325.

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